Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 6-7-04
Art Unit: 1614 Phone Number ~~30~~ 272-0587 Serial Number: 09/988,285
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MEJ

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A composition comprising

1) acridine derivatives
2) camptothecin derivatives

The acridine derivative is selected from

C-F120918, XR9051 or XR9576

The camptothecin derivatives selected from

topotecan BNP1350 CPT11
GC211 9-aminocamptothecin
DX8951f 9-nitrocamptothecin

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: R. Puppel	NA Sequence (#)_____	STN C
Searcher Phone #: 2-2557	AA Sequence (#)_____	Dialog _____
Searcher Location: 1665	Structure (#) _____	Questel/Orbit: _____
Date Searcher Picked Up: 6/11/04	Bibliographic _____	Dr.Link _____
Date Completed: 6/15/04	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time: _____	Other _____	Other (specify) _____

PTO-1590 (1-2000)

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=> b reg
FILE 'REGISTRY' ENTERED AT 10:09:36 ON 15 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   14 JUN 2004  HIGHEST RN 693217-50-4
DICTIONARY FILE UPDATES:  14 JUN 2004  HIGHEST RN 693217-50-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l13
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L6             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  BNP 1350/CN
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L10            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9-NITROCAMPTOTHECIN/CN
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L12            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  XR 9576/CN
L13           12 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L1 OR L2 OR L3 OR L4 OR L5
                  OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12)


=> d ide l13 1-12

L13  ANSWER 1 OF 12  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   206873-63-4  REGISTRY
CN   3-Quinolinecarboxamide, N-[2-[[[4-[2-(3,4-dihydro-6,7-dimethoxy-2(1H)-
     isoquinolinyl)ethyl]phenyl]amino]carbonyl]-4,5-dimethoxyphenyl]- (9CI)
     (CA INDEX NAME)
OTHER NAMES:
CN   Tariquidar
CN   XR 9576
FS   3D CONCORD
MF   C38 H38 N4 O6
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, CA, CAPLUS, EMBASE, IMSDRUGNEWS,
       IMSPATENTS, IMSRESEARCH, MEDLINE, MRCK*, PHAR, PROUSDDR, SYNTHLINE,
       TOXCENTER, USAN, USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Journal; Patent
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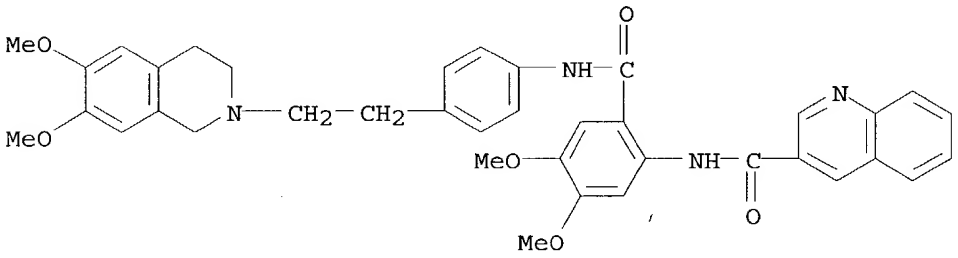
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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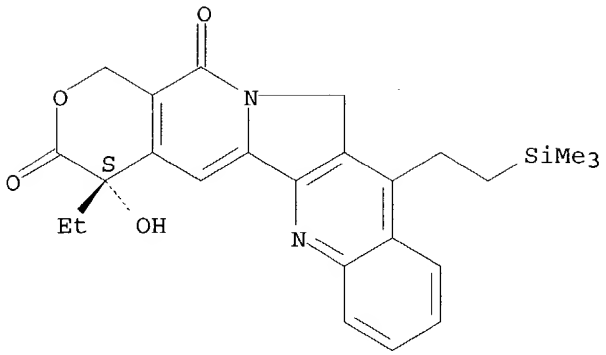
RN 203923-89-1 REGISTRY
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-11-[2-(trimethylsilyl)ethyl]-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-11-[2-(trimethylsilyl)ethyl]-, (S)-
OTHER NAMES:
CN **BNP 1350**
CN DB 172
CN Karenitecin
FS STEREOSEARCH
MF C25 H28 N2 O4 Si
SR CA
LC STN Files: ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); USES (Uses)

Absolute stereochemistry.



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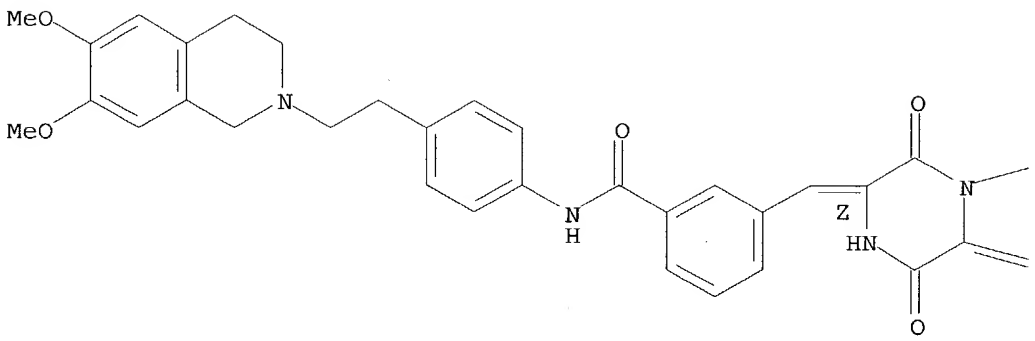
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 180422-22-4 REGISTRY
CN Benzamide, N-[4-[2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)ethyl]phenyl]-3-[(Z)-[(5Z)-4-methyl-3,6-dioxo-5-(phenylmethylene)piperazinylidene]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Benzamide, N-[4-[2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)ethyl]phenyl]-3-[[4-methyl-3,6-dioxo-5-(phenylmethylene)piperazinylidene]methyl]-, monohydrochloride, (Z,Z)-
OTHER NAMES:
CN **XR 9051**
FS STEREOSEARCH
MF C39 H38 N4 O5 . Cl H
SR CA
LC STN Files: CA, CAPLUS, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); USES (Uses)

Double bond geometry as shown.

PAGE 1-A



● HCl

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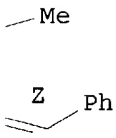

13 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 169869-90-3 REGISTRY
CN 10H,13H-Benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione, 1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-, (1S,9S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 10H,13H-Benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione, 1-amino-9-ethyl-5-fluoro-1,2,3,9,12,15-hexahydro-9-hydroxy-4-methyl-, (1S-trans)-, monomethanesulfonate (salt)
OTHER NAMES:
CN **DX 8951f**
CN Exatecan mesylate
FS STEREOSEARCH
DR 251459-30-0
MF C24 H22 F N3 O4 . C H4 O3 S
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, CA, CAPLUS, CASREACT, CIN, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Conference; Journal; Patent

Searched by P. Ruppel

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)

CM 1

CRN 171335-80-1
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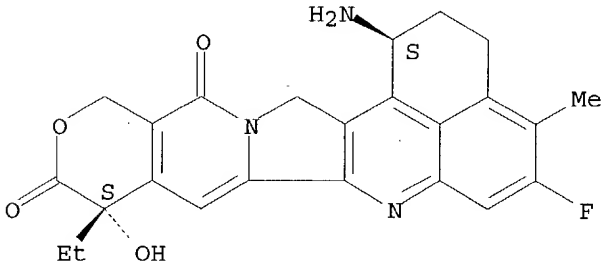
Absolute stereochemistry.



CM 2

CRN 75-75-2
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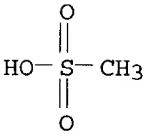

50 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
51 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 149882-10-0 REGISTRY
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (8S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (S)-
OTHER NAMES:
CN **GG 211**
CN GI 147211
CN Lurtotecan
CN NX 211
CN OSI 211
FS STEREOSEARCH

MF C28 H30 N4 O6
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
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RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
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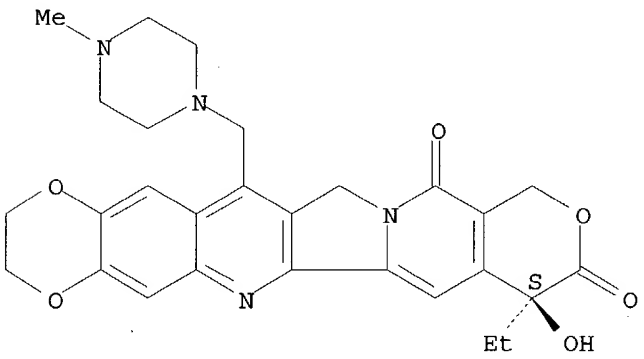
Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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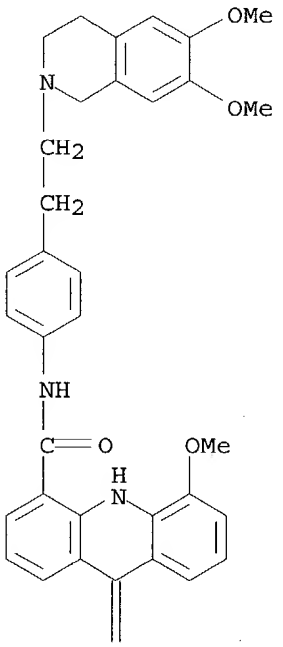
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
60 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 143664-11-3 REGISTRY
CN 4-Acridinecarboxamide, N-[4-[2-(3,4-dihydro-6,7-dimethoxy-2(1H)-isoquinolinyl)ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Elacridar
CN **GF 120918**
CN GG 918
CN GW 0918
FS 3D CONCORD
MF C34 H33 N3 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ANABSTR, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
Other Sources: WHO

DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

PAGE 1-A



PAGE 2-A

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

87 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
88 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 123948-87-8 REGISTRY
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-, (S)-

OTHER NAMES:
CN 10-Hydroxy-9-[(dimethylamino)methyl]-(20S)-camptothecin
CN 9-(N,N-Dimethylaminomethyl)-10-hydroxycamptothecin
CN Hycamptamine
CN Hycamptin
CN NSC 609699
CN SKF 104864
CN SKF-S 104864
CN **Topotecan**
CN Topotecan lactone
FS STEREOSEARCH
DR 133242-28-1, 138121-88-7
MF C23 H23 N3 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CIN, DDFU, DIOGENES, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent
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RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
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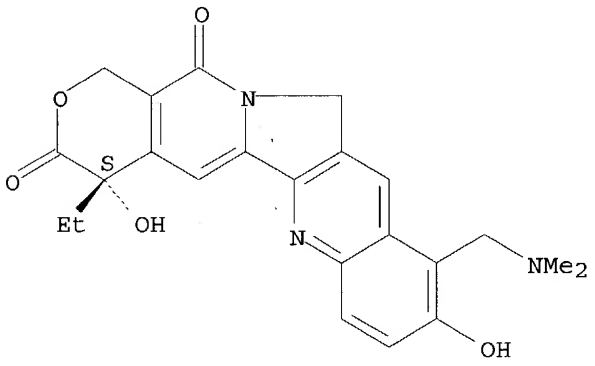
Absolute stereochemistry.



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1049 REFERENCES IN FILE CA (1907 TO DATE)
29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1057 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 100286-90-6 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride, (S)-
OTHER NAMES:
CN 7-Ethyl-10-[[4-(1-piperidyl)-1-piperidyl]carbonyloxy]camptothecin hydrochloride
CN Campto
CN Camptothecin 11
CN Camptothecin 11 hydrochloride
CN **CPT 11**
CN Irinotecan hydrochloride
CN Topotecin
CN U 101440E
FS STEREOSEARCH
DR 111348-33-5
MF C33 H38 N4 O6 . Cl H
SR CA
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(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Journal; Patent
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RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
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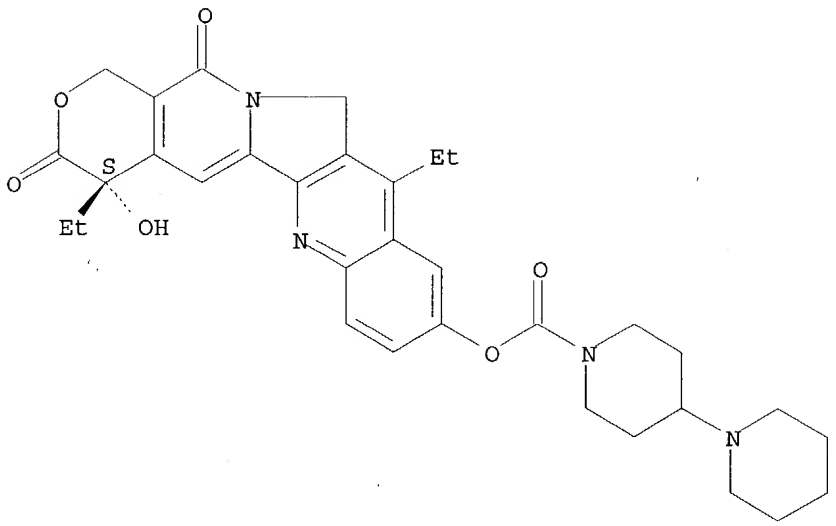
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 2-A

● HCl

597 REFERENCES IN FILE CA (1907 TO DATE)
9 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
598 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 91421-43-1 REGISTRY
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-amino-4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 10-amino-4-ethyl-4-hydroxy-, (S)-
OTHER NAMES:
CN 9-Amino-20(S)-camptothecin
CN **9-Aminocamptothecin**
CN NSC 603071
FS STEREOSEARCH
MF C20 H17 N3 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, CSCHEM, IMSDRUGNEWS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Journal; Patent; Report
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

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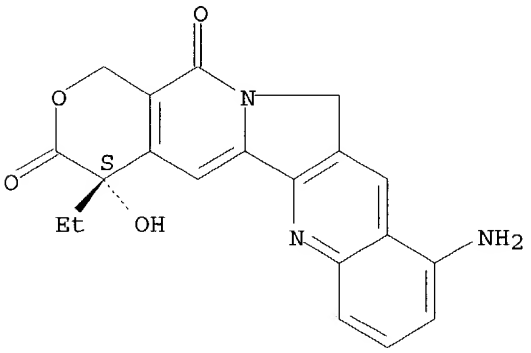
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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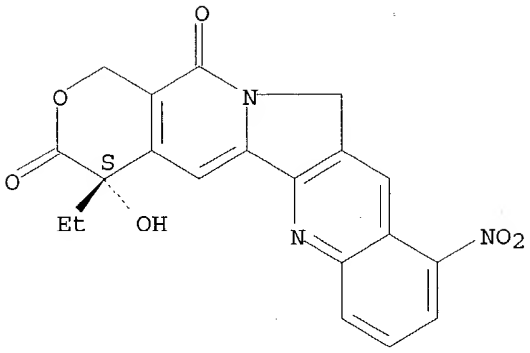
257 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 91421-42-0 REGISTRY
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-10-nitro-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-10-nitro-, (S)-
OTHER NAMES:
CN 9-Nitro-20(S)-camptothecin
CN **9-Nitrocamptothecin**
CN RFS 2000
CN Rubitecan
FS STEREOSEARCH
MF C20 H15 N3 O6
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



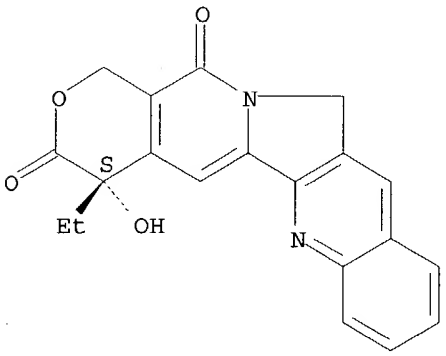
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

189 REFERENCES IN FILE CA (1907 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
190 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L13 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 7689-03-4 REGISTRY
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (S)-
CN Camptothecine (7CI)
OTHER NAMES:
CN (+)-Camptothecin
CN (+)-Camptothecine
CN (S)-Camptothecin
CN 20(S)-Camptothecin
CN 20(S)-Camptothecine
CN **Camptothecin**
CN d-Camptothecin
CN NSC 94600
FS STEREOSEARCH
DR 30628-51-4, 157405-40-8
MF C20 H16 N2 O4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological

study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry. Rotation (+).

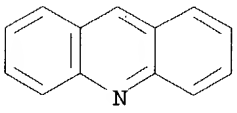


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2398 REFERENCES IN FILE CA (1907 TO DATE)
342 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2413 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L13 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN
RN 260-94-6 REGISTRY
CN **Acridine (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 10-Azaanthracene
CN 2,3-Benzoquinoline
CN 9-Azaanthracene
CN Benzo[b]quinoline
CN Dibenzo[b,e]pyridine
CN NSC 3408
FS 3D CONCORD
MF C13 H9 N
CI COM, RPS
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties);

RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4156 REFERENCES IN FILE CA (1907 TO DATE)
421 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4159 REFERENCES IN FILE CAPLUS (1907 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> => b zcaplus
FILE 'ZCAPLUS' ENTERED AT 11:02:53 ON 15 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 15 Jun 2004 VOL 140 ISS 25
FILE LAST UPDATED: 14 Jun 2004 (20040614/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que l21
L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON ACRIDINE/CN
L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON GF 120918/CN
L3 1 SEA FILE=REGISTRY ABB=ON PLU=ON XR 9051/CN
L4 1 SEA FILE=REGISTRY ABB=ON PLU=ON CAMPTOTHECIN/CN

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L5              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  TOPOTECAN/CN
L6              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  BNP 1350/CN
L7              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CPT 11/CN
L8              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  GG 211/CN
L9              1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9-AMINOCAMPTOTHECIN/CN
L10             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9-NITROCAMPTOTHECIN/CN
L11             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DX 8951F/CN
L12             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  XR 9576/CN
L14          1005 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L1(L)?DERIVATIVE?/BI
L15           102 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  (L2 OR L3) OR L12
L16          1106 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L14 OR L15
L17           258 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L4(L)?DERIVATIVE?/BI
L18          1877 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  (L5 OR L6 OR L7 OR L8 OR L9
                  OR L10 OR L11)
L19          2035 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L17 OR L18
L20            15 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L16 AND L19
L21             5 SEA FILE=ZCAPLUS ABB=ON   PLU=ON  L20 AND (PY<=1999 OR PRY<=1999
                   OR AY<=1999)


=> b medl
FILE 'MEDLINE' ENTERED AT 11:03:12 ON 15 JUN 2004

 FILE LAST UPDATED: 12 JUN 2004 (20040612/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l39
L22 (        348)SEA FILE=MEDLINE ABB=ON  PLU=ON  ACRIDINE?(2A)DERIVATIVE?
L23 (        460)SEA FILE=MEDLINE ABB=ON  PLU=ON  ACRIDINE/CT,CN OR L22
L24 (         57)SEA FILE=MEDLINE ABB=ON  PLU=ON  "GF 120918"/CN
L25 (          2)SEA FILE=MEDLINE ABB=ON  PLU=ON  "XR 9051"/CN
L26 (         11)SEA FILE=MEDLINE ABB=ON  PLU=ON  TARIQUIDAR/CN
L27 (        526)SEA FILE=MEDLINE ABB=ON  PLU=ON  (L23 OR L24 OR L25 OR L26)
L28 (       3517)SEA FILE=MEDLINE ABB=ON  PLU=ON  CAMPTOTHECIN/CN
L29 (          0)SEA FILE=MEDLINE ABB=ON  PLU=ON  L28(L)AA
L30 (        860)SEA FILE=MEDLINE ABB=ON  PLU=ON  TOPOTECAN/CN
L31 (          6)SEA FILE=MEDLINE ABB=ON  PLU=ON  "BNP 1350"/CN
L32 (       1564)SEA FILE=MEDLINE ABB=ON  PLU=ON  IRINOTECAN/CN
L33 (          3)SEA FILE=MEDLINE ABB=ON  PLU=ON  GG(2A)211
L34 (         35)SEA FILE=MEDLINE ABB=ON  PLU=ON  "DX 8951"/CN
L35 (         99)SEA FILE=MEDLINE ABB=ON  PLU=ON  9-AMINO-20-CAMPTOTHECIN/CN
L36 (         73)SEA FILE=MEDLINE ABB=ON  PLU=ON  9-NITROCAMPTOTHECIN/CN
L37 (        312)SEA FILE=MEDLINE ABB=ON  PLU=ON  CAMPTOTHECIN?(2A)?DERIVATIVE?/
                  BI
L38 (       2613)SEA FILE=MEDLINE ABB=ON  PLU=ON  (L29 OR L30 OR L31 OR L32 OR
                  L33 OR L34 OR L35 OR L36 OR L37)
L39             5 SEA FILE=MEDLINE ABB=ON  PLU=ON  L27 AND L38


=> b embase
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FILE 'EMBASE' ENTERED AT 11:03:22 ON 15 JUN 2004
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 FILE COVERS 1974 TO 10 Jun 2004 (20040610/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l78
L40 (      5550)SEA FILE=EMBASE ABB=ON  PLU=ON  ACRIDINE/CN OR ACRIDINE? OR
                ACRIDINE(2A)?DERIVATIVE?/BI
L41 (       148)SEA FILE=EMBASE ABB=ON  PLU=ON  "GF 120918"/CN OR GF(W)120918
L42 (       147)SEA FILE=EMBASE ABB=ON  PLU=ON  ELACRIDAR/CT
L43 (       180)SEA FILE=EMBASE ABB=ON  PLU=ON  L42 OR L41
L44 (         7)SEA FILE=EMBASE ABB=ON  PLU=ON  "XR 9051"/CN
L45 (         7)SEA FILE=EMBASE ABB=ON  PLU=ON  "XR 9051"/CT
L46 (         7)SEA FILE=EMBASE ABB=ON  PLU=ON  XR(W)9051
L47 (         7)SEA FILE=EMBASE ABB=ON  PLU=ON  (L44 OR L45 OR L46)
L48 (        54)SEA FILE=EMBASE ABB=ON  PLU=ON  "XR 9576"/CN
L49 (        64)SEA FILE=EMBASE ABB=ON  PLU=ON  TARIQUIDAR/CT OR "XR 9576"/CT
L50 (        58)SEA FILE=EMBASE ABB=ON  PLU=ON  XR(W)9576
L51 (        64)SEA FILE=EMBASE ABB=ON  PLU=ON  (L48 OR L49 OR L50)
L52 (      5724)SEA FILE=EMBASE ABB=ON  PLU=ON  L40 OR L43 OR L47 OR L51
L53 (      2502)SEA FILE=EMBASE ABB=ON  PLU=ON  CAMPTOTHECIN/CT
L54 (       839)SEA FILE=EMBASE ABB=ON  PLU=ON  CAMPTOTHECIN(2A)?DERIVATIVE?/BI

L55 (      3448)SEA FILE=EMBASE ABB=ON  PLU=ON  CAMPTOTHECIN?
L56 (      3448)SEA FILE=EMBASE ABB=ON  PLU=ON  (L53 OR L54 OR L55)
L57 (      2675)SEA FILE=EMBASE ABB=ON  PLU=ON  TOPOTECAN/CT
L58 (      2734)SEA FILE=EMBASE ABB=ON  PLU=ON  TOPOTECAN? OR TOPOTECAN(2A)?DER
                IVATIVE?/BI
L59 (      2734)SEA FILE=EMBASE ABB=ON  PLU=ON  L57 OR L58
L60 (        21)SEA FILE=EMBASE ABB=ON  PLU=ON  "BNP 1350"/CT
L61 (        20)SEA FILE=EMBASE ABB=ON  PLU=ON  "BNP 1350"/CN
L62 (        21)SEA FILE=EMBASE ABB=ON  PLU=ON  L60 OR L61
L63 (      1355)SEA FILE=EMBASE ABB=ON  PLU=ON  "CPT 11"/CN
L64 (      4130)SEA FILE=EMBASE ABB=ON  PLU=ON  IRINOTECAN/CT
L65 (      4189)SEA FILE=EMBASE ABB=ON  PLU=ON  IRINOTECAN?
L66 (      4189)SEA FILE=EMBASE ABB=ON  PLU=ON  L64 OR L65
L67 (      4189)SEA FILE=EMBASE ABB=ON  PLU=ON  L66 OR L63
L68 (        13)SEA FILE=EMBASE ABB=ON  PLU=ON  "GG 211"/CN
L69 (        84)SEA FILE=EMBASE ABB=ON  PLU=ON  (LURTOTECAN/CT OR "GG 211"/CT
                OR "GI 147211"/CT)
L70 (        14)SEA FILE=EMBASE ABB=ON  PLU=ON  GG(W)211
L71 (        84)SEA FILE=EMBASE ABB=ON  PLU=ON  L69 OR L70
L72 (        65)SEA FILE=EMBASE ABB=ON  PLU=ON  "DX 8951F"/CN
L73 (       272)SEA FILE=EMBASE ABB=ON  PLU=ON  ?AMINOCAMPTOTHECIN?
L74 (        94)SEA FILE=EMBASE ABB=ON  PLU=ON  ?NITROCAMPTOTHECIN?
L75 (      8543)SEA FILE=EMBASE ABB=ON  PLU=ON  L56 OR L59 OR L62 OR L67 OR
                L68 OR L69 OR L71 OR L72 OR L73 OR L74
L76 (       117)SEA FILE=EMBASE ABB=ON  PLU=ON  L52 AND L75
L77 (     14420)SEA FILE=EMBASE ABB=ON  PLU=ON  DRUG BIOAVAILABILITY/CT
L78           10 SEA FILE=EMBASE ABB=ON  PLU=ON  L76 AND L77


=> b ipa
FILE 'IPA' ENTERED AT 11:03:35 ON 15 JUN 2004
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FILE COVERS 1970 TO 2 JUN 2004 (20040602/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> d que l99
L79 (        11) SEA FILE=IPA ABB=ON  PLU=ON  (ACRIDINE/CT OR "ACRIDINE
                 DERIVATIVES"/CT OR "ACRIDINE DERIVATIVES, SYNTHESIS"/CT)
L82           3  SEA FILE=IPA ABB=ON  PLU=ON  GF-120918/CT
L83           0  SEA FILE=IPA ABB=ON  PLU=ON  XR-9051/CT
L84           0  SEA FILE=IPA ABB=ON  PLU=ON  XR-9576/CT
L85          46  SEA FILE=IPA ABB=ON  PLU=ON  TOPOTECAN/CT
L86           0  SEA FILE=IPA ABB=ON  PLU=ON  XR-9576
L87          75  SEA FILE=IPA ABB=ON  PLU=ON  (TOPOTECAN/CT OR "TOPOTECAN
                 HYDROCHLORIDE"/CT OR "TOPOTECAN HYDROCHLORIDE, APPROVALS"/CT
                 OR "TOPOTECAN HYDROCHLORIDE, CHROMATOGRAPHY, LIQUID"/CT OR
                 "TOPOTECAN HYDROCHLORIDE, CONTAMINATION"/CT OR "TOPOTECAN
                 HYDROCHLORIDE, EQUILIBRIUM CONSTANTS"/CT OR "TOPOTECAN
                 HYDROCHLORIDE, FORMULATIONS"/CT OR "TOPOTECAN HYDROCHLORIDE,
                 INCOMPATIBILITIES"/CT OR "TOPOTECAN HYDROCHLORIDE, INJECTIONS"/
                 CT OR "TOPOTECAN HYDROCHLORIDE, LIPOSOMES"/CT OR "TOPOTECAN
                 HYDROCHLORIDE, NEOPLASMS"/CT OR "TOPOTECAN HYDROCHLORIDE,
                 OVARIAN NEOPLASMS"/CT OR "TOPOTECAN HYDROCHLORIDE, OVERVIEW"/CT
                  OR "TOPOTECAN HYDROCHLORIDE, PHARMACOKINETICS"/CT OR "TOPOTECA
                 N HYDROCHLORIDE, REVIEW"/CT OR "TOPOTECAN HYDROCHLORIDE,
                 TOXICITY"/CT OR "TOPOTECAN, ADVERSE REACTIONS"/CT OR "TOPOTECAN
                 , AVAILABILITY"/CT OR "TOPOTECAN, BREAST NEOPLASMS"/CT OR
                 "TOPOTECAN, CARCINOMA"/CT OR "TOPOTECAN, CONTAMINATION"/CT OR
                 "TOPOTECAN, DOSAGE"/CT OR "TOPOTECAN, DOSAGE SCHEDULES"/CT OR
                 "TOPOTECAN, ENDOMETRIAL NEOPLASMS"/CT OR "TOPOTECAN, GERIATRICS
                 "/CT OR "TOPOTECAN, INJECTIONS"/CT OR "TOPOTECAN, LEUKEMIA"/CT
                 OR "TOPOTECAN, LUNG NEOPLASMS"/CT OR "TOPOTECAN, MECHANISM OF
                 ACTION"/CT OR "TOPOTECAN, MENINGEAL NEOPLASMS"/CT OR "TOPOTECAN
                 , NEOPLASMS"/CT OR "TOPOTECAN, OVARIAN NEOPLASMS"/CT OR
                 "TOPOTECAN, OVERVIEW"/CT OR "TOPOTECAN, PHARMACOECONOMICS"/CT
                 OR "TOPOTECAN, PHARMACOKINETICS"/CT OR "TOPOTECAN, REVIEW"/CT
                 OR "TOPOTECAN, SALIVA LEVELS"/CT OR "TOPOTECAN, TOXICITY"/CT
                 OR "TOPOTECAN, TOXICITY, ENVIRONMENTAL"/CT)
L88           0  SEA FILE=IPA ABB=ON  PLU=ON  BNP-1350/CT
L89          18  SEA FILE=IPA ABB=ON  PLU=ON  CPT-11/CT OR "IRINOTECAN HYDROCHLO
                 RIDE ANHYDROUS"/CT
L90           0  SEA FILE=IPA ABB=ON  PLU=ON  GG-211/CT
L91           9  SEA FILE=IPA ABB=ON  PLU=ON  9-AMINOCAMPTOTHECIN/CT
L92           2  SEA FILE=IPA ABB=ON  PLU=ON  9-NITROCAMPTOTHECIN/CT
L93           0  SEA FILE=IPA ABB=ON  PLU=ON  DX-8951F/CT
L94           4  SEA FILE=IPA ABB=ON  PLU=ON  L79(L)DERIVATIVE?
L95           7  SEA FILE=IPA ABB=ON  PLU=ON  L94 OR (L82 OR L83 OR L84)
L97          14  SEA FILE=IPA ABB=ON  PLU=ON  CAMPTOTHECIN(2A)DERIVATIVE?
L98         107  SEA FILE=IPA ABB=ON  PLU=ON  L97 OR (L85 OR L86 OR L87 OR L88
                 OR L89 OR L90 OR L91 OR L92 OR L93)
L99           1  SEA FILE=IPA ABB=ON  PLU=ON  L95 AND L98


=> b biosis
FILE 'BIOSIS' ENTERED AT 11:03:49 ON 15 JUN 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 9 June 2004 (20040609/ED)

FILE RELOADED: 19 October 2003.

=> d que l124
L100(       199)SEA FILE=BIOSIS ABB=ON  PLU=ON  ACRIDINE/CT OR ("ACRIDINE
                DERIVATIVE"/CT OR "ACRIDINE DERIVATIVES"/CT)
L101(       432)SEA FILE=BIOSIS ABB=ON  PLU=ON  ACRIDINE(2A)?DERIVATIVE?/BI
L102(       568)SEA FILE=BIOSIS ABB=ON  PLU=ON  L100 OR L101
L103(        11)SEA FILE=BIOSIS ABB=ON  PLU=ON  "GF 120918"/CT OR GF-120918/CT

L104(        17)SEA FILE=BIOSIS ABB=ON  PLU=ON  GF(W)120918
L105(        17)SEA FILE=BIOSIS ABB=ON  PLU=ON  L103 OR L104
L106(         1)SEA FILE=BIOSIS ABB=ON  PLU=ON  XR-9051/CT
L107(         2)SEA FILE=BIOSIS ABB=ON  PLU=ON  XR(W)9051
L108(         2)SEA FILE=BIOSIS ABB=ON  PLU=ON  L106 OR L107
L109(         6)SEA FILE=BIOSIS ABB=ON  PLU=ON  "XR 9576"/CT
L110(         8)SEA FILE=BIOSIS ABB=ON  PLU=ON  XR(W)9576
L111(         8)SEA FILE=BIOSIS ABB=ON  PLU=ON  L109 OR L110
L112(       595)SEA FILE=BIOSIS ABB=ON  PLU=ON  L102 OR L105 OR L108 OR L111
L113(      1830)SEA FILE=BIOSIS ABB=ON  PLU=ON  CAMPTOTHECIN/CT OR ("CAMPTOTHEC
                IN ANALOG"/CT OR "CAMPTOTHECIN ANALOG COMPOUNDS"/CT OR
                "CAMPTOTHECIN ANALOG-CARBOXYMETHYL DEXTRAN CONJUGATE"/CT OR
                "CAMPTOTHECIN ANALOGS"/CT OR "CAMPTOTHECIN ANALOGUE"/CT OR
                "CAMPTOTHECIN ANALOGUES"/CT) OR ("CAMPTOTHECIN COMPOSITION"/CT
                OR "CAMPTOTHECIN COMPOUNDS"/CT OR "CAMPTOTHECIN CONJUGATES"/CT
                OR "CAMPTOTHECIN DERIVATIVE"/CT OR "CAMPTOTHECIN DERIVATIVE
                INTERMEDIATES"/CT OR "CAMPTOTHECIN DERIVATIVE-CARBOXYMETHYL
                DEXTRAN CONJUGATE"/CT OR "CAMPTOTHECIN DERIVATIVE-CARBOXYMETHYL
                DEXTRAN CONJUGATE"/CT OR "CAMPTOTHECIN DERIVATIVE-PLATIN
                DERIVATIVE COMPOSITION"/CT OR "CAMPTOTHECIN DERIVATIVE-POLYMERI
                C CONJUGATES"/CT OR "CAMPTOTHECIN DERIVATIVES"/CT OR "CAMPTOTHE
                CIN DERIVATIVES PREPARATION INTERMEDIATE"/CT OR "CAMPTOTHECIN
                DERIVATVE"/CT OR "CAMPTOTHECIN DRUG"/CT OR "CAMPTOTHECIN
                DRUGS"/CT OR "CAMPTOTHECIN GLUCOCONJUGATE"/CT OR "CAMPTOTHECIN
                GLYCOCONJUGATE"/CT)
L114(       359)SEA FILE=BIOSIS ABB=ON  PLU=ON  CAMPTOTHECIN(2A)?DERIVATIVE?/BI

L115(      1993)SEA FILE=BIOSIS ABB=ON  PLU=ON  L113 OR L114
L116(      1452)SEA FILE=BIOSIS ABB=ON  PLU=ON  TOPOTECAN
L117(        17)SEA FILE=BIOSIS ABB=ON  PLU=ON  BNP1350 OR BNP(2A)1350
L118(      1177)SEA FILE=BIOSIS ABB=ON  PLU=ON  CPT11 OR CPT(2A)11
L119(         7)SEA FILE=BIOSIS ABB=ON  PLU=ON  GG211 OR GG(2A)211
L120(        43)SEA FILE=BIOSIS ABB=ON  PLU=ON  DX(2A)8951F OR DX8951F
L121(       160)SEA FILE=BIOSIS ABB=ON  PLU=ON  ?AMINOCAMPTOTHECIN?
L122(       102)SEA FILE=BIOSIS ABB=ON  PLU=ON  ?NITROCAMPTOTHECIN?
L123(      4348)SEA FILE=BIOSIS ABB=ON  PLU=ON  (L115 OR L116 OR L117 OR L118
                OR L119 OR L120 OR L121 OR L122)
L124           5 SEA FILE=BIOSIS ABB=ON  PLU=ON  L112 AND L123


=> b wpix
FILE 'WPIX' ENTERED AT 11:04:16 ON 15 JUN 2004
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FILE LAST UPDATED:          11 JUN 2004      <20040611/UP>
MOST RECENT DERWENT UPDATE:     200437        <200437/DW>
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    NEW FORMAT GERMAN PATENT APPLICATION AND PUBLICATION
    NUMBERS. SEE ALSO:
    http://www.stn-international.de/archive/stnews/news0104.pdf <<<

=> d que l153
L125(      3517)SEA FILE=MEDLINE ABB=ON  PLU=ON  CAMPTOTHECIN/CN
L126(         0)SEA FILE=MEDLINE ABB=ON  PLU=ON  L125(L)AA
L127(       860)SEA FILE=MEDLINE ABB=ON  PLU=ON  TOPOTECAN/CN
L128(         6)SEA FILE=MEDLINE ABB=ON  PLU=ON  "BNP 1350"/CN
L129(      1564)SEA FILE=MEDLINE ABB=ON  PLU=ON  IRINOTECAN/CN
L130(         3)SEA FILE=MEDLINE ABB=ON  PLU=ON  GG(2A)211
L131(        35)SEA FILE=MEDLINE ABB=ON  PLU=ON  "DX 8951"/CN
L132(        99)SEA FILE=MEDLINE ABB=ON  PLU=ON  9-AMINO-20-CAMPTOTHECIN/CN
L133(        73)SEA FILE=MEDLINE ABB=ON  PLU=ON  9-NITROCAMPTOTHECIN/CN
L134(       312)SEA FILE=MEDLINE ABB=ON  PLU=ON  CAMPTOTHECIN?(2A)?DERIVATIVE?/
                BI
L135(      2613)SEA FILE=MEDLINE ABB=ON  PLU=ON  (L126 OR L127 OR L128 OR L129
                OR L130 OR L131 OR L132 OR L133 OR L134)
L136(       187)SEA FILE=WPIX ABB=ON  PLU=ON  (ACRIDINE(W)?DERIVATIVE?)/BIX
L137(         9)SEA FILE=WPIX ABB=ON  PLU=ON  (GF120918 OR GF(2A)120918)/BIX
L138(         4)SEA FILE=WPIX ABB=ON  PLU=ON  (XR9051 OR XR(2A)9051)/BIX
L139(         4)SEA FILE=WPIX ABB=ON  PLU=ON  (XR9576 OR XR(2A)9576)/BIX
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L141(       685)SEA FILE=WPIX ABB=ON  PLU=ON  CAMPTOTHECIN
L142(       222)SEA FILE=WPIX ABB=ON  PLU=ON  CAMPTOTHECIN(2A)?DERIVATIVE?/BIX

L143(       251)SEA FILE=WPIX ABB=ON  PLU=ON  TOPOTECAN
L144(         1)SEA FILE=WPIX ABB=ON  PLU=ON  BNP1350 OR BNP(2A)1350
L145(       100)SEA FILE=WPIX ABB=ON  PLU=ON  CPT11 OR CPT(2A)11
L146(         3)SEA FILE=WPIX ABB=ON  PLU=ON  GG211 OR GG(2A)211
L147(         6)SEA FILE=WPIX ABB=ON  PLU=ON  DX8951F OR DX(2A)8951F
L148(        31)SEA FILE=WPIX ABB=ON  PLU=ON  ?AMINOCAMPTOTHECIN?
L149(        32)SEA FILE=WPIX ABB=ON  PLU=ON  ?NITROCAMPTOTHECIN?
L150(       230)SEA FILE=WPIX ABB=ON  PLU=ON  (L127 OR L128 OR L129 OR L130 OR
                L131 OR L132 OR L133 OR L134 OR L135)
L151(       865)SEA FILE=WPIX ABB=ON  PLU=ON  (L141 OR L142 OR L143 OR L144 OR
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                L145 OR L146 OR L147 OR L148 OR L149)
L152(        871) SEA FILE=WPIX ABB=ON  PLU=ON  L150 OR L151
L153           3 SEA FILE=WPIX ABB=ON  PLU=ON  L140 AND L152


=> dup rem l124 l39 l21 l78 l99 l153
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PROCESSING COMPLETED FOR L78
PROCESSING COMPLETED FOR L99
PROCESSING COMPLETED FOR L153
L154          25 DUP REM L124 L39 L21 L78 L99 L153 (4 DUPLICATES REMOVED)

=> d all l154 1-25

L154 ANSWER 1 OF 25     MEDLINE on STN
AN   2004082800     MEDLINE
DN   PubMed ID: 14973080
TI   Pheophorbide a is a specific probe for ABCG2 function and inhibition.
AU   Robey Robert W; Steadman Kenneth; Polgar Orsolya; Morisaki Kuniaki;
     Blayney Margaret; Mistry Prakash; Bates Susan E
CS   Cancer Therapeutics Branch, Center for Cancer Research, National Cancer
     Institute, National Institutes of Health, Building 10, Rm. 12C203, 9000
     Rockville Pike, Bethesda, MD 20892, USA.. robeyr@mail.nih.gov
SO   Cancer research, (2004 Feb 15) 64 (4) 1242-6.
     Journal code: 2984705R. ISSN: 0008-5472.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200404
ED   Entered STN: 20040220
     Last Updated on STN: 20040403
     Entered Medline: 20040402
AB   Pheophorbide a (PhA), a chlorophyll catabolite, was shown to be an ABCG2
     substrate based on Abcg2(-/-) knockout mouse studies (J. W. Jonker et
     al., Proc. Natl. Acad. Sci. USA, 99: 15649-15654, 2002). We developed
     a functional assay for ABCG2 using PhA and the ABCG2 inhibitor
     fumitremorgin C. In selected cell lines expressing high levels of
     P-glycoprotein, multidrug resistance-associated protein 1, or ABCG2, PhA
     transport was observed only in cells expressing ABCG2. Fumitremorgin
```

C-inhibitable PhA transport was found to correlate with cell surface ABCG2 expression as measured by the anti-ABCG2 antibody 5D3. We found that 100 micro M of the cyclin-dependent kinase inhibitor UCN-01 or 1 micro M of the P-glycoprotein inhibitor tariquidar inhibited ABCG2-mediated PhA transport. In 4-day cytotoxicity assays, ABCG2-mediated resistance to SN-38 and topotecan was abrogated in ABCG2-transfected HEK-293 cells treated with 1 micro M tariquidar, and ABCG2-transfected cells were 6-7-fold resistant to UCN-01. PhA is an ABCG2-specific substrate with potential value in measuring ABCG2 function and expression in clinical samples.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*ATP-Binding Cassette Transporters: AI, antagonists & inhibitors
*ATP-Binding Cassette Transporters: PH, physiology
Breast Neoplasms: DT, drug therapy
*Camptothecin: AA, analogs & derivatives
Camptothecin: PD, pharmacology
*Chlorophyll: AA, analogs & derivatives
*Chlorophyll: ME, metabolism
Drug Resistance, Neoplasm
*Neoplasm Proteins: AI, antagonists & inhibitors
*Neoplasm Proteins: PH, physiology
Quinolines: PD, pharmacology
*Staurosporine: AA, analogs & derivatives
Staurosporine: PD, pharmacology
Topotecan: PD, pharmacology

RN 112953-11-4 (7-hydroxystaurosporine); **123948-87-8 (Topotecan)**; 1406-65-1 (Chlorophyll); 15664-29-6 (pheophorbide a); **206873-63-4 (tariquidar)**; 62996-74-1 (Staurosporine); 7689-03-4 (Camptothecin); 86639-52-3 (7-ethyl-10-hydroxycamptothecin)

CN 0 (ABCG2 protein, human); 0 (ATP-Binding Cassette Transporters); 0 (Neoplasm Proteins); 0 (Quinolines)

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AN 2004105539 EMBASE

TI Drug transport at the blood-brain barrier and the choroid plexus.

AU Graff C.L.; Pollack G.M.

CS G.M. Pollack, Division of Drug Delivery, Disposition School of Pharmacy, University of North Carolina, Kerr Hall, Chapell Hill, NC 27599-7360, United States. gary_pollack@unc.edu

SO Current Drug Metabolism, (2004) 5/1 (95-108).
Refs: 170
ISSN: 1389-2002 CODEN: CDMUBU

CY Netherlands

DT Journal; General Review

FS 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB The blood-brain barrier (BBB) and blood-CSF barrier (BCSFB) represent the main interfaces between the central nervous system (CNS) and the peripheral circulation. Drug exposure to the CNS is dependent on a variety of factors, including the physical barrier presented by the BBB and the BCSFB and the affinity of the substrate for specific transport systems located at both of these interfaces. It is the aggregate effect of these factors that ultimately determines the total CNS exposure, and thus pharmacological efficacy, of a drug or drug candidate. This review discusses the anatomical and biochemical barriers presented to solute

access to the CNS. In particular, the important role played by various efflux transporters in the overall barrier function is considered in detail, as current literature suggests that efflux transport likely represents a key determinant of overall CNS exposure for many substrates. Finally, it is important to consider not only the net delivery of the agent to the CNS, but also the ability of the agent to access the relevant target site within the CNS. Potential approaches to increasing both net CNS and target-site exposure, when such exposure is dictated by efflux transport, are considered.

CT Medical Descriptors:
*drug transport
*blood brain barrier
*choroid plexus
biochemistry
solute
central nervous system function
drug exposure
drug delivery system
drug targeting
blood cerebrospinal fluid barrier
drug mechanism
drug efficacy
pain: DT, drug therapy
drug penetration
dose response
drug absorption
drug disposition
drug clearance
drug bioavailability
drug protein binding
drug sensitivity
transport kinetics
human
nonhuman
review
Drug Descriptors:
amino acid transporter: EC, endogenous compound
levodopa: PD, pharmacology
gabapentin: PD, pharmacology
glucose transporter 1: EC, endogenous compound
metenkephalin: PD, pharmacology
glycoprotein P
enkephalin[2,5 dextro penicillamine]: DV, drug development
enkephalin[2,5 dextro penicillamine]: DO, drug dose
enkephalin[2,5 dextro penicillamine]: DT, drug therapy
enkephalin[2,5 dextro penicillamine]: PK, pharmacokinetics
enkephalin[2,5 dextro penicillamine]: PD, pharmacology
enkephalin[2,5 dextro penicillamine]: IV, intravenous drug administration
elacridar: PD, pharmacology
loperamide: CB, drug combination
loperamide: CR, drug concentration
loperamide: IT, drug interaction
loperamide: PK, pharmacokinetics
loperamide: PD, pharmacology
quinidine: CB, drug combination
quinidine: IT, drug interaction
quinidine: PD, pharmacology
breast cancer resistance protein: EC, endogenous compound
topotecan: PK, pharmacokinetics
topotecan: PO, oral drug administration

mitoxantrone: PK, pharmacokinetics
RNA directed DNA polymerase inhibitor: PD, pharmacology
multidrug resistance protein: EC, endogenous compound
probenecid: PD, pharmacology
indometacin: PD, pharmacology
mercaptopurine: PD, pharmacology
tioguanine: PD, pharmacology
adefovir: PD, pharmacology
organic cation transporter: EC, endogenous compound
carnitine: PD, pharmacology
mepyramine: PD, pharmacology
organic anion transporter: EC, endogenous compound
digoxin: PD, pharmacology
estrone sulfate: PD, pharmacology
azathioprine: PD, pharmacology
tricyclic antidepressant agent: PD, pharmacology
penicillin G: PD, pharmacology
unindexed drug

RN (levodopa) 59-92-7; (gabapentin) 60142-96-3; (glucose transporter 1) 172077-08-6; (metenkephalin) 58569-55-4; (enkephalin[2,5 dextro penicillamine]) 88373-73-3, 88381-29-7; (elacridar) 143664-11-3; (loperamide) 34552-83-5, 53179-11-6; (quinidine) 56-54-2; (**topotecan**) 119413-54-6, 123948-87-8; (mitoxantrone) 65271-80-9, 70476-82-3; (multidrug resistance protein) 149200-37-3, 208997-77-7; (probenecid) 57-66-9; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (tioguanine) 154-42-7; (adefovir) 106941-25-7; (carnitine) 461-06-3, 541-15-1, 56-99-5; (mepyramine) 6036-95-9, 91-84-9; (digoxin) 20830-75-5, 57285-89-9; (estrone sulfate) 438-67-5, 481-97-0; (azathioprine) 446-86-6; (penicillin G) 1406-05-9, 61-33-6

CN **Gf 120918**

L154 ANSWER 3 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2004028443 EMBASE

TI Multidrug resistance in cancer chemotherapy and xenobiotic protection mediated by the half ATP-binding cassette transporter ABCG2.

AU Han B.; Zhang J.-T.

CS J.-T. Zhang, Dept. of Pharmacology and Toxicology, IUCC, Indiana Univ. School of Medicine, 1044 W. Walnut Street, Indianapolis, IN 46202, United States. jianzhan@iupui.edu

SO Current Medicinal Chemistry - Anti-Cancer Agents, (2004) 4/1 (31-42). Refs: 74
ISSN: 1568-0118 CODEN: CMCACI

CY Netherlands

DT Journal; General Review

FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB ABCG2, also termed BCRP/MXR/ABCP, is a half ATP-binding cassette (ABC) transporter expressed on plasma membranes. ABCG2 was independently cloned from placenta as well as cell lines selected for resistance to mitoxantrone or anthracyclines. ABCG2 consists of a nucleotide-binding domain (NBD) at the amino terminus and a transmembrane domain (TMD) at the carboxyl terminus and it is postulated to form a homodimer to perform its biological functions. Over-expression of ABCG2 in cell lines confers resistance on a wide variety of anticancer drugs including mitoxantrone,

daunorubicin, doxorubicin, **topotecan** and epirubicin. The expression of ABCG2 has been implicated in multidrug resistance (MDR) of acute myeloid leukemia and some solid tumors. In addition, ABCG2 can transport several fluorescent dyes or toxins. ABCG2 is found to be expressed in epithelial cells of intestine and colon, liver canaliculi, and renal tubules, where it serves to eliminate the plasma level of orally administered anticancer drugs as well as ingested toxins. ABCG2 is found to be highly expressed in placenta and the luminal surface of microvessel endothelium blood-brain barrier where it may play a role in limiting the penetration of drugs, such as **topotecan** from the maternal plasma into the fetus and from blood to brain. A variety of inhibitors for ABCG2 including GF120918 may prove useful for sensitizing cancer cells to chemotherapy or altering the distribution of orally administered drug substrates of ABCG2. Interestingly, ABCG2 is also expressed highly in hematopoietic stem cells. However, the function of ABCG2 in stem cells is currently unknown, although it may provide protection to stem cells from a variety of xenobiotics.

CT Medical Descriptors:
*multidrug resistance
*cancer chemotherapy
protein expression
molecular cloning
nucleotide binding site
amino terminal sequence
carboxy terminal sequence
gene overexpression
cell line
acute granulocytic leukemia: DR, drug resistance
solid tumor: DR, drug resistance
intestine epithelium cell
colon mucosa
intrahepatic bile duct
kidney tubule
vascular endothelium
blood brain barrier
maternal plasma
hematopoietic stem cell
cell protection
drug blood level
drug penetration
drug bioavailability
drug transport
drug structure
drug distribution
drug mechanism
drug potentiation
human
nonhuman
review
nucleotide sequence
Drug Descriptors:
*xenobiotic agent: AN, drug analysis
*xenobiotic agent: CR, drug concentration
*xenobiotic agent: IT, drug interaction
*xenobiotic agent: PK, pharmacokinetics
*xenobiotic agent: PD, pharmacology
*xenobiotic agent: IV, intravenous drug administration
*xenobiotic agent: PO, oral drug administration
*breast cancer resistance protein: EC, endogenous compound
placenta protein: EC, endogenous compound

mitoxantrone: PK, pharmacokinetics
anthracycline derivative: PK, pharmacokinetics
membrane protein: EC, endogenous compound
antineoplastic agent: AN, drug analysis
antineoplastic agent: CR, drug concentration
antineoplastic agent: PK, pharmacokinetics
antineoplastic agent: IV, intravenous drug administration
antineoplastic agent: PO, oral drug administration
daunorubicin: PK, pharmacokinetics
doxorubicin: PK, pharmacokinetics
topotecan: IT, drug interaction
topotecan: PK, pharmacokinetics
topotecan: IV, intravenous drug administration
topotecan: PO, oral drug administration
elacridar: AN, drug analysis
elacridar: PK, pharmacokinetics
epirubicin: PK, pharmacokinetics
fluorescent dye
toxin
prazosin: PK, pharmacokinetics
etoposide: PK, pharmacokinetics
teniposide: PK, pharmacokinetics
irinotecan: PK, pharmacokinetics
9 aminocamptothecin: PK, pharmacokinetics
7 ethyl 10 hydroxycamptothecin: IT, drug interaction
7 ethyl 10 hydroxycamptothecin: PK, pharmacokinetics
7 ethyl 10 hydroxycamptothecin: PD, pharmacology
6 formylamino 12,13 dihydro 1,11 dihydroxy 5h indolo[2,3 a]pyrrolo[3,4 c]carbazole 5,7(6h) dione 13 glucoside: PK, pharmacokinetics
cytotoxic agent: AN, drug analysis
cytotoxic agent: CR, drug concentration
cytotoxic agent: IT, drug interaction
cytotoxic agent: PK, pharmacokinetics
cytotoxic agent: PD, pharmacology
cytotoxic agent: IV, intravenous drug administration
cytotoxic agent: PO, oral drug administration
flavopiridol: PK, pharmacokinetics
bisantrene: PK, pharmacokinetics
methotrexate: PK, pharmacokinetics
zidovudine: PK, pharmacokinetics
pheophorbide: AN, drug analysis
pheophorbide: PK, pharmacokinetics
reserpine: AN, drug analysis
reserpine: PK, pharmacokinetics
reserpine: PD, pharmacology
tamoxifen: AN, drug analysis
tamoxifen: PK, pharmacokinetics
unindexed drug

RN (mitoxantrone) 65271-80-9, 70476-82-3; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (doxorubicin) 23214-92-8, 25316-40-9; (**topotecan**) 119413-54-6, 123948-87-8; (elacridar) 143664-11-3; (epirubicin) 56390-09-1, 56420-45-2; (prazosin) 19216-56-9, 19237-84-4; (etoposide) 33419-42-0; (teniposide) 29767-20-2; (**irinotecan**) 100286-90-6; (7 ethyl 10 hydroxycamptothecin) 86639-52-3; (6 formylamino 12,13 dihydro 1,11 dihydroxy 5h indolo[2,3 a]pyrrolo[3,4 c]carbazole 5,7(6h) dione 13 glucoside) 151069-12-4; (flavopiridol) 146426-40-6; (bisantrene) 71439-68-4, 78186-34-2; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (zidovudine) 30516-87-1; (reserpine) 50-55-5, 8001-95-4; (tamoxifen) 10540-29-1

CN **Gf 120918**; **Cpt 11**; Sn 38; Nb 506

GEN GENBANK AAA82056 referred number; GENBANK AAC97367 referred number; GENBANK AAG40003 referred number; GENBANK AAG40004 referred number; GENBANK AAK14241 referred number; GENBANK AAO13805 referred number; GENBANK CAA36038 referred number; GENBANK CAA62631 referred number; GENBANK NP_036050 referred number; GENBANK NP_071452 referred number; GENBANK NP_114090 referred number; GENBANK P12428 referred number; GENBANK Q64343 referred number

L154 ANSWER 4 OF 25 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-381415 [36] WPIX
DNC C2003-101173
TI Mucoadhesive vaginal composition for treating cancer comprises chemotherapeutic agent, lipophilic or hydrophilic carrier, mucoadhesive agent and sorption promoter.
DC A96 B05 B07 P32
IN BENET, L Z; LIU, J H; PAULETTI, G M; RITSCHEL, W A
PA (BENE-I) BENET L Z; (LIUJ-I) LIU J H; (PAUL-I) PAULETTI G M; (RITS-I) RITSCHEL W A; (UMDU-N) UMD INC
CYC 100
PI WO 2003020210 A2 20030313 (200336)* EN 61 A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
US 2003049302 A1 20030313 (200336) A61K009-22
ADT WO 2003020210 A2 WO 2002-US27027 20020821; US 2003049302 A1 Provisional US 2001-315877P 20010829, US 2002-226667 20020821
PRAI US 2001-315877P 20010829; US 2002-226667 20020821
IC ICM A61K000-00; A61K009-22
ICS A61F006-06
AB WO2003020210 A UPAB: 20030609
NOVELTY - A mucoadhesive vaginal composition comprises a chemotherapeutic agent, a lipophilic or hydrophilic carrier, a mucoadhesive agent and a sorption promoter.

DETAILED DESCRIPTION - A mucoadhesive vaginal composition comprises: a chemotherapeutic agent (0.001 - 3000 mg) (preferably daunorubicin, doxorubicin, idarubicin, amrubicin, pirarubicin, epirubicin, mitoxantrone, etoposide, teniposide, vinblastine, vincristine, mitomycin C, paclitaxel, docetaxel, actinomycin D, colchicine, **topotecan**, irinotecan or gemcitabine; or a membrane efflux system inhibitor (preferably cyclosporin, verapamil, valspodor, biricodar, quinidine, terfenadine, pervilleine A, **GF120918**, LY335979, OC144-093, **XR9576**, probenecid and/or MK571); a lipophilic or hydrophilic carrier (30 - 95) % (preferably saturated mono-, di- and/or triglyceride of 8-18C fatty acid, polyethylene glycol (having molecular weight of 200 - 800)) and/or their derivative; a mucoadhesive agent (5 - 25) % (preferably cellulose derivative, natural gum, alginate or pectin); and a sorption promoter (5 - 25) % (preferably non-ionizable glycol ester derivative, glycol derivative with glycerol ester, non-ionizable glycol ether derivative or an inter-esterified stone oil).

An INDEPENDENT CLAIM is included for a medicated intravaginal device for transmucosal delivery of chemotherapeutic agents and membrane efflux system inhibitors comprising (C1).

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - For treating cancer in human females (claimed) (e.g. ovarian, cervical and uterine cancer).

ADVANTAGE - The composition allows systemic circulation of the drug

and permits administration of lower concentrations of the drug. The composition prevents leaking of the drug out of the vagina, which results in greater systemic bioavailability compared to that after oral administration; and enhances transmucosal absorption of chemotherapeutic agents. The vaginal delivery of inhibitor of membrane efflux system further reduces the risk of toxic side effects following administration to cancer patients diagnosed with drug-resistant tumors. The method avoids intravenous administration, permits extended or controlled continuous or pulsed delivery of the chemotherapeutic agents and/or inhibitors of membrane efflux system and thus achieves delivery of higher concentration of the drug.

Dwg.1/17

FS CPI GMPI
FA AB; GI; DCN
MC CPI: A12-V01; B02-Z; B04-A02; B04-B03A; B04-C01; B04-C02A; B04-C02D; B04-C03C; B06-H; B07-H; B10-A08; B11-C04; B12-M02B; B12-M03; B12-M08; B12-M11C; B12-M11E; B12-M11F; B14-H01B

L154 ANSWER 5 OF 25 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-553619 [52] WPIX
DNC C2003-149550
TI New use of **acridine derivative** for inhibiting mitoxantrone resistance transporter in treatment of e.g. cancer, acute lymphocytic leukemia and non-Hodgkin's lymphoma.
DC B02 B04 D16
IN BATES, S; ROBEY, R
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 6521635 B1 20030218 (200352)* 27 A61K031-435
ADT US 6521635 B1 Provisional US 2000-177410P 20000120, US 2001-767594 20010122
PRAI US 2000-177410P 20000120; US 2001-767594 20010122
IC ICM A61K031-435
AB US 6521635 B UPAB: 20030813

NOVELTY - Use of an **acridine derivative** (I), or its salt or solvate, for inhibiting a mitoxantrone resistance (MXR) transporter in a cell overexpressing MXR gene but not overexpressing a P-glycoprotein (Pgp) gene, by contacting with the cell, is new.

DETAILED DESCRIPTION - Use of an **acridine derivative** of formula (I), or its salt or solvate, for inhibiting a mitoxantrone resistance (MXR) transporter in a cell overexpressing MXR gene but not overexpressing a P-glycoprotein (Pgp) gene, by contacting with the cell, is new.

Ra = R1, amino or nitro;
R1 = H, halo, 1-4C alkyl, 1-4C alkoxy or 1-4C alkylthio;
R2 = H or 1-4C alkyl;
A = O, S or a bond;
B' = unsubstituted 1-4C alkylene; and
R3, R4 = 1-4C alkoxy.

INDEPENDENT CLAIMS are also included for the following:

(1) assaying the modulation of the functional effect of a test compound on the cell by (I), comprising contacting the test compound with the cells in the presence and absence of (I) and measuring the ability of (I) to modulate the functional effect of the test compound; and

(2) treatment of cancer that overexpresses the (MXR) gene but not overexpresses the (Pgp) gene, comprising co-administering a chemotherapeutic recognized by the MXR transporter and (I).

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - MXR transporter inhibitor; Pgp antagonist; Multidrug resistance gene 1 (MDR-1)-inhibitor; Cancer cell growth

inhibitor.

Colon cancer cell line (S1-M1-80) (2000 cells/well), mitoxantrone and N-(4-(2-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl)-phenyl)-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide (A) were added to a 96-well plate. Control was prepared without (A), and it was incubated at 37 deg. C for 96 hours. After incubation, the cells were fixed and stained with sulforhodamine B, and IC50 was determined. The IC50 (micro M) of mitoxantrone, without and with (A) (1 micro M), was 222 plus or minus 101 and 0.12 plus or minus 0.11, respectively. The results showed that (A) sensitized S1-M1-80 cells expressing MXR by 1850-fold.

USE - For inhibiting the MXR transporter, and for treating cancer (e.g. lung cancer, colon cancer, breast cancer, prostate cancer, acute lymphocytic leukemia, non-Hodgkin's lymphoma and ovarian cancer) (claimed).

ADVANTAGE - (I) Is a potent multispecific antagonist capable of inhibiting or reversing both Pgp-mediated and MXR-mediate multidrug resistance phenotype.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B02-D; B04-F01; B06-D03; B06-D11; B06-E05; B08-D02; B11-C08E; B12-K04E; B14-H01; B14-L06; D05-H09

L154 ANSWER 6 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2003195141 EMBASE

TI Pharmacogenomics of ABC transporters and its role in cancer chemotherapy.

AU Sparreboom A.; Danesi R.; Ando Y.; Chan J.; Figg W.D.

CS W.D. Figg, Clinical Pharmacology Research Core, Center for Cancer Research, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892, United States. wdfigg@helix.nih.gov

SO Drug Resistance Updates, (2003) 6/2 (71-84).

Refs: 135

ISSN: 1368-7646 CODEN: DRUPFW

CY United Kingdom

DT Journal; (Short Survey)

FS 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB ATP-binding cassette (ABC) genes play a role in the resistance of malignant cells to anticancer agents. The ABC gene products, including ABCB1 (P-glycoprotein), ABCC1 (MRP1), ABCC2 (MRP2, cMOAT), and ABCG2 (BCRP, MXR, ABCP) are also known to influence oral absorption and disposition of a wide variety of drugs. As a result, the expression levels of these proteins in humans have important consequences for an individual's susceptibility to certain drug-induced side effects, interactions, and treatment efficacy. Naturally occurring variants in ABC transporter genes have been identified that might affect the function and expression of the protein. This review focuses on recent advances in the pharmacogenomics of ABC transporters, and discusses potential implications of genetic variants for the chemotherapeutic treatment of cancer.

CT Medical Descriptors:
*pharmacogenomics
*cancer chemotherapy
*multidrug resistance
cancer cell

drug absorption
drug disposition
protein expression
protein blood level
drug sensitivity
drug efficacy
protein function
genetic variability
protein motif
protein domain
genetic code
gene mapping
chromosome 7q
phenotype
drug transport
blood brain barrier
cell type
epithelium cell
drug bioavailability
chromosome 16p
drug conjugation
knockout mouse
drug hypersensitivity
dendritic cell
chromosome 10q
gene mutation
anion transport
protein localization
gene identification
gene function
detoxification
genetic screening
gene sequence
wild type
exon
missense mutation
genetic analysis
Dubin Johnson syndrome
genotype
drug metabolism
oxidative stress
rhabdomyosarcoma: DR, drug resistance
human
nonhuman
short survey
priority journal
Drug Descriptors:
*antineoplastic agent: AD, drug administration
*antineoplastic agent: PO, oral drug administration
*gene product: EC, endogenous compound
*ABC transporter: EC, endogenous compound
glycoprotein P: EC, endogenous compound
multidrug resistance protein 1: EC, endogenous compound
multidrug resistance protein 2: EC, endogenous compound
glutathione
etoposide: TO, drug toxicity
leukotriene C4: EC, endogenous compound
radixin: EC, endogenous compound
mitoxantrone
anthracycline

topotecan
doxorubicin
protein: EC, endogenous compound
breast cancer resistance protein: EC, endogenous compound
mitoxantrone resistance protein: EC, endogenous compound
dye
digoxin: CR, drug concentration
digoxin: IV, intravenous drug administration
digoxin: PO, oral drug administration
tsukubaenolide: CR, drug concentration
cyclosporin
vincristine
valspodar: PD, pharmacology
biricodar: PD, pharmacology
dactinomycin
daunorubicin
cyclosporin A
chlorambucil
clotrimazole
unindexed drug
unclassified drug
xr 9576

RN (multidrug resistance protein 2) 256503-65-8; (glutathione) 70-18-8; (etoposide) 33419-42-0; (leukotriene C4) 72025-60-6; (mitoxantrone) 65271-80-9, 70476-82-3; (**topotecan**) 119413-54-6, 123948-87-8; (doxorubicin) 23214-92-8, 25316-40-9; (protein) 67254-75-5; (digoxin) 20830-75-5, 57285-89-9; (tsukubaenolide) 104987-11-3; (cyclosporin) 79217-60-0; (vincristine) 57-22-7; (valspodar) 121584-18-7; (biricodar) 174254-13-8; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (cyclosporin A) 59865-13-3, 63798-73-2; (chlorambucil) 305-03-3; (clotrimazole) 23593-75-1

CN **Xr 9576**

L154 ANSWER 7 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2003030753 EMBASE

TI Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: An overview.

AU Schinkel A.H.; Jonker J.W.

CS A.H. Schinkel, Division of Experimental Therapy, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands. a.schinkel@nki.nl

SO Advanced Drug Delivery Reviews, (21 Jan 2003) 55/1 (3-29). Refs: 169
ISSN: 0169-409X CODEN: ADDREP

PUI S 0169-409X(02)00169-2

CY Netherlands

DT Journal; General Review

FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LA English

SL English

AB Active drug efflux transporters of the ATP binding cassette (ABC)-containing family of proteins have a major impact on the pharmacological behavior of most of the drugs in use today. Pharmacological properties affected by ABC transporters include the oral bioavailability, hepatobiliary, direct intestinal, and urinary excretion of drugs and drug-metabolites and -conjugates. Moreover, the penetration

of drugs into a range of important pharmacological sanctuaries, such as brain, testis, and fetus, and the penetration into specific cell- and tissue compartments can be extensively limited by ABC transporters. These interactions with ABC transporters determine to a large extent the clinical usefulness, side effects and toxicity risks of drugs. Many other xenotoxins, (pre-)carcinogens and endogenous compounds are also influenced by the ABC transporters, with corresponding consequences for the well-being of the individual. We aim to provide an overview of properties of the mammalian ABC transporters known to mediate significant transport of clinically relevant drugs.

CT Medical Descriptors:
drug transport
protein family
drug bioavailability
hepatobiliary system
intestine absorption
urinary excretion
drug excretion
drug penetration
drug conjugation
blood brain barrier
fetomaternal transfusion
toxicity
risk factor
protein function
blood testis barrier
kidney
tissue distribution
protein localization
drug degradation
ataxia: SI, side effect
transport kinetics
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*ABC transporter: EC, endogenous compound
breast cancer resistance protein: EC, endogenous compound
multidrug resistance protein 1: EC, endogenous compound
multidrug resistance protein 2: EC, endogenous compound
multidrug resistance protein 3: EC, endogenous compound
multidrug resistance protein 4: EC, endogenous compound
multidrug resistance protein 5: EC, endogenous compound
glycoprotein P: EC, endogenous compound
asimadoline
morphine
vinblastine
vincristine
paclitaxel
docetaxel: PK, pharmacokinetics
docetaxel: IV, intravenous drug administration
doxorubicin: DO, drug dose
doxorubicin: IT, drug interaction
doxorubicin: PK, pharmacokinetics
doxorubicin: IP, intraperitoneal drug administration
daunorubicin
epirubicin

bisantrene
mitoxantrone
etoposide: DO, drug dose
etoposide: IT, drug interaction
etoposide: PK, pharmacokinetics
etoposide: IP, intraperitoneal drug administration
valspodar: AE, adverse drug reaction
valspodar: CT, clinical trial
valspodar: DO, drug dose
valspodar: IT, drug interaction
valspodar: PK, pharmacokinetics
valspodar: PO, oral drug administration
elacridar: CT, clinical trial
elacridar: CM, drug comparison
elacridar: DO, drug dose
elacridar: IT, drug interaction
elacridar: PK, pharmacokinetics
elacridar: PD, pharmacology
elacridar: PO, oral drug administration
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: CT, clinical trial
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: CM, drug comparison
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: IT, drug interaction
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: PK, pharmacokinetics
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: IP, intraperitoneal drug administration
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: IV, intravenous drug administration
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: PO, oral drug administration
protein inhibitor: AE, adverse drug reaction
protein inhibitor: CT, clinical trial
protein inhibitor: DO, drug dose
protein inhibitor: IT, drug interaction
protein inhibitor: PK, pharmacokinetics
protein inhibitor: IV, intravenous drug administration
protein inhibitor: PO, oral drug administration
xr 9576: IT, drug interaction
xr 9576: IV, intravenous drug administration
xr 9576: PO, oral drug administration
oc 144 093: IT, drug interaction
oc 144 093: IV, intravenous drug administration
oc 144 093: PO, oral drug administration
saquinavir: IT, drug interaction
topotecan
7 ethyl 10 hydroxycamptothecin
unindexed drug
unclassified drug

RN (multidrug resistance protein 2) 256503-65-8; (multidrug resistance protein 3) 231947-64-1; (multidrug resistance protein 4) 299244-49-8; (multidrug resistance protein 5) 266988-95-8; (asimadoline) 153205-46-0; (morphine) 52-26-6, 57-27-2; (vinblastine) 865-21-4; (vincristine) 57-22-7; (paclitaxel) 33069-62-4; (docetaxel) 114977-28-5; (doxorubicin) 23214-92-8, 25316-40-9; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (epirubicin) 56390-09-1, 56420-45-2; (bisantrene) 71439-68-4, 78186-34-2; (mitoxantrone) 65271-80-9, 70476-82-3; (etoposide) 33419-42-0; (valspodar) 121584-18-7; (elacridar) 143664-11-3; (1 [4 (11,11

difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol) 167465-36-3; (saquinavir) 127779-20-8, 149845-06-7; (**topotecan**) 119413-54-6, 123948-87-8; (7 ethyl 10 hydroxycamptothecin) 86639-52-3
CN Sdz psc 833; **Gf 120918**; Ly 335979; Sn 38; Oc 144 093

L154 ANSWER 8 OF 25 MEDLINE on STN
AN 2002346178 MEDLINE
DN PubMed ID: 12089219
TI Boosting bioavailability of topotecan: what do we gain?.
CM Comment on: J Clin Oncol. 2002 Jul 1;20(13):2943-50. PubMed ID: 12089223
Comment in: J Clin Oncol. 2003 Jan 1;21(1):177; author reply 177. PubMed ID: 12506192
AU Hudes Gary
SO Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2002 Jul 1) 20 (13) 2918-9.
Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT Commentary
Editorial
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020629
Last Updated on STN: 20030116
Entered Medline: 20020715
CT Check Tags: Female; Human
*ATP-Binding Cassette Transporters: AI, antagonists & inhibitors
*Acridines: PD, pharmacology
Administration, Oral
Antineoplastic Agents: AD, administration & dosage
*Antineoplastic Agents: PK, pharmacokinetics
Biological Availability
Breast Neoplasms: DT, drug therapy
*Breast Neoplasms: ME, metabolism
*DNA Topoisomerases, Type I: AI, antagonists & inhibitors
Drug Resistance, Multiple
Drug Resistance, Neoplasm
Enzyme Inhibitors: AD, administration & dosage
*Enzyme Inhibitors: PK, pharmacokinetics
Intestinal Absorption: DE, drug effects
*Isoquinolines: PD, pharmacology
Neoplasm Proteins: AI, antagonists & inhibitors
*P-Glycoprotein: AI, antagonists & inhibitors
*Tetrahydroisoquinolines
Topotecan: AD, administration & dosage
*Topotecan: PK, pharmacokinetics
RN **123948-87-8 (Topotecan); 143664-11-3 (GF 120918)**
CN 0 (ABCG2 protein, human); 0 (ATP-Binding Cassette Transporters); 0 (Acridines); 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Isoquinolines); 0 (Neoplasm Proteins); 0 (P-Glycoprotein); 0 (Tetrahydroisoquinolines); EC 5.99.1.2 (DNA Topoisomerases, Type I)

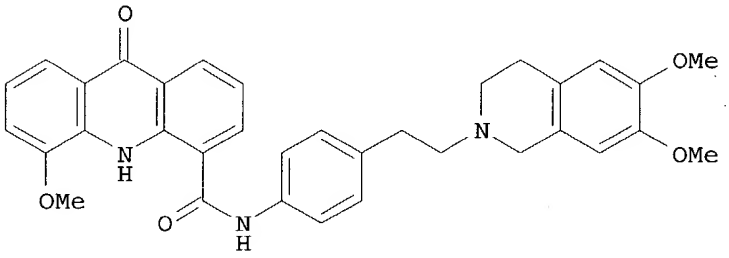
L154 ANSWER 9 OF 25 ZCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:696659 ZCAPLUS
DN 137:222100
ED Entered STN: 13 Sep 2002
TI Improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compositions
IN Schellens, Johannes Henricus Matthias; Schinkel, Alfred Hermanus

PA Netherlands Cancer Institute, Neth.
SO U.S. Pat. Appl. Publ., 11 pp., Cont.-in-part of Appl. No. PCT/NL00/00331.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-517
ICS A61K031-4745; A61K031-473; A61K031-47; A61K031-12
NCL 514297000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002128282	A1	20020912	US 2001-988285	20011119 <--
WO 2000069390	A2	20001123	WO 2000-NL331	20000517 <--
WO 2000069390	A3	20011213		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI NL 1999-1012066 A 19990517 <--
NL 1999-1012481 A 19990630 <--
WO 2000-NL331 A2 20000517
GI



I

AB A method for increasing the systemic exposure of cells selected from tumor cells and normal cells to an orally administered pharmaceutically active compound, wherein a bioenhancer comprising an inhibitor of BCRP (breast cancer resistance protein) is orally administered concomitantly with said orally administered pharmaceutically active compound, and in which method the inhibitor is administered simultaneously with the pharmaceutical compound Coadministration of a single oral dose of GF120918 (I) results in a profoundly increased systemic exposure to oral topotecan.

ST drug delivery oral bioavailability enhancer
IT Multidrug resistance proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BCRP (breast cancer resistance protein); improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)
IT Antitumor agents
Drug bioavailability
Human

(improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

IT Mycotoxins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

IT Drug delivery systems
(oral; improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

IT 56-65-5, Atp, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binding to; improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

IT **123948-87-8**, Topotecan **143664-11-3**, GF120918
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

IT 84-65-1D, Anthraquinone, derivs. 19216-56-9, Prazosin 65271-80-9, Mitoxantrone 86639-52-3, Sn38 **91421-42-0**, 9-Nitrocamptothecin **91421-43-1**, 9-Aminocamptothecin **100286-90-6**, Cpt11 118974-02-0, Fumitremorgin C **149882-10-0**, GG211 **169869-90-3**, DX8951f **180422-22-4**, XR 9051 **203923-89-1**, BNP1350 **206873-63-4**, XR 9576
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and oral drug delivery compns.)

L154 ANSWER 10 OF 25 MEDLINE on STN DUPLICATE 1
AN 2002346182 MEDLINE
DN PubMed ID: 12089223
TI Increased oral bioavailability of topotecan in combination with the breast cancer resistance protein and P-glycoprotein inhibitor GF120918.
CM Comment in: J Clin Oncol. 2002 Jul 1;20(13):2918-9. PubMed ID: 12089219
AU Kruijtzer C M F; Beijnen J H; Rosing H; ten Bokkel Huinink W W; Schot M; Jewell R C; Paul E M; Schellens J H M
CS Department of Medical Oncology, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands.
SO Journal of clinical oncology : official journal of the American Society of Clinical Oncology, (2002 Jul 1) 20 (13) 2943-50.
Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020629
Last Updated on STN: 20020716
Entered Medline: 20020715
AB PURPOSE: We discovered that breast cancer resistance protein (BCRP), a recently identified adenosine triphosphate-binding cassette drug transporter, substantially limits the oral bioavailability of topotecan in mdr1a/1b(-/-) P-glycoprotein (P-gp) knockout and wild-type mice. GF120918 is a potent inhibitor of BCRP and P-gp. The aim was to increase the bioavailability of topotecan by GF120918. PATIENTS AND METHODS: In cohort A, eight patients received 1.0 mg/m(2) oral topotecan with or without

coadministration of one single oral dose of 1,000 mg GF120918 (day 1 or day 8). In cohort B, eight other patients received 1.0 mg/m(2) intravenous topotecan with or without 1,000 mg oral GF120918 to study the effect of GF120918 on the systemic clearance of topotecan. RESULTS: After oral topotecan, the mean area under the plasma concentration-time curve (AUC) of total topotecan increased significantly from 32.4 +/- 9.6 microg.h/L without GF120918 to 78.7 +/- 20.6 microg.h/L when GF120918 was coadministered (P =.008). The mean maximum plasma concentration of total topotecan increased from 4.1 +/- 1.5 microg/L without GF120918 to 11.5 +/- 2.4 microg/L with GF120918 (P =.008). The apparent bioavailability in this cohort increased significantly from 40.0% (range, 32% to 47%) to 97.1% (range, 91% to 120%) (P =.008). Interpatient variability of the apparent bioavailability was 17% without and 11% with GF120918. After intravenous administration of topotecan, coadministration of oral GF120918 had a small but statistically significant effect on the AUC and systemic clearance of total topotecan but no statistically significant effect on maximum plasma concentration and terminal half-life of total topotecan. CONCLUSION: Coadministration of the BCRP and P-gp inhibitor GF120918 resulted in a significant increase of the systemic exposure of oral topotecan. The apparent oral bioavailability increased from 40.0% without to 97.1% with GF120918.

CT Check Tags: Female; Human
*ATP-Binding Cassette Transporters: AI, antagonists & inhibitors
Acridines: PD, pharmacology
*Acridines: TU, therapeutic use
Administration, Oral
Adult
Antineoplastic Agents: AD, administration & dosage
*Antineoplastic Agents: PK, pharmacokinetics
Biological Availability
*Breast Neoplasms: DT, drug therapy
*Breast Neoplasms: ME, metabolism
Drug Administration Schedule
Drug Resistance, Multiple
Drug Resistance, Neoplasm
Enzyme Inhibitors: AD, administration & dosage
*Enzyme Inhibitors: PK, pharmacokinetics
Isoquinolines: PD, pharmacology
*Isoquinolines: TU, therapeutic use
Middle Aged
Neoplasm Proteins: AI, antagonists & inhibitors
*P-Glycoprotein: AI, antagonists & inhibitors
*Tetrahydroisoquinolines
Topotecan: AD, administration & dosage
*Topotecan: PK, pharmacokinetics

RN **123948-87-8 (Topotecan); 143664-11-3 (GF 120918)**

CN 0 (ABCG2 protein, human); 0 (ATP-Binding Cassette Transporters); 0 (Acridines); 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Isoquinolines); 0 (Neoplasm Proteins); 0 (P-Glycoprotein); 0 (Tetrahydroisoquinolines)

L154 ANSWER 11 OF 25 EMBASE on STN

AN 2002410079 EMBASE

TI Oral cancer treatment: Developments in chemotherapy and beyond.

AU O'Neill V.J.; Twelves C.J.

CS C.J. Twelves, Cancer Res. UK Dept. of Med. Oncol., University of Glasgow, Alexander Stone Building, Switchback Road, Glasgow G6I IBD, United Kingdom. c.twelves@beatson.gla.ac.uk

SO British Journal of Cancer, (21 Oct 2002) 87/9 (933-937).

Refs: 24
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LA English
SL English
AB Oncology is one of the few areas of medicine where most patients are treated intravenously rather than receiving oral drugs. Recently, several oral anti-cancer drugs have been approved and there are many more in development. Oral chemotherapy is attractive because of its convenience and ease of administration, particularly in the palliative setting. With an increasing number of oral agents emerging, we can expect to see a rapid rise in the use of oral chemotherapy in years to come. This article reviews recent developments in oral chemotherapy, both of traditional cytotoxics and novel, targeted agents, from the viewpoint of patients, physicians, drug developers and health-care providers. .COPYRGT. 2002 Cancer Research UK.
CT Medical Descriptors:
*cancer combination chemotherapy
*mouth cancer: DM, disease management
*mouth cancer: DT, drug therapy
drug approval
cancer palliative therapy
drug formulation
lung small cell cancer: DT, drug therapy
drug efficacy
diarrhea: SI, side effect
bone marrow suppression: SI, side effect
toxicity: SI, side effect
drug hypersensitivity: SI, side effect
antineoplastic activity
drug activity
drug absorption
cardiotoxicity: SI, side effect
drug bioavailability
rash: SI, side effect
acne: SI, side effect
nausea: SI, side effect
drug targeting
molecular mechanics
drug infusion
vomiting: SI, side effect
patient compliance
health care system
health care cost
drug cost
human
clinical trial
review
priority journal
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: AD, drug administration
*antineoplastic agent: CB, drug combination

*antineoplastic agent: IT, drug interaction
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: PE, pharmacoeconomics
*antineoplastic agent: PR, pharmaceutics
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: PD, pharmacology
*antineoplastic agent: IV, intravenous drug administration
*antineoplastic agent: PO, oral drug administration
cytotoxic agent: AE, adverse drug reaction
cytotoxic agent: CT, clinical trial
cytotoxic agent: AD, drug administration
cytotoxic agent: CB, drug combination
cytotoxic agent: IT, drug interaction
cytotoxic agent: DT, drug therapy
cytotoxic agent: PR, pharmaceutics
cytotoxic agent: PK, pharmacokinetics
cytotoxic agent: PD, pharmacology
cytotoxic agent: IV, intravenous drug administration
cytotoxic agent: PO, oral drug administration
topotecan: AE, adverse drug reaction
topotecan: AD, drug administration
topotecan: DT, drug therapy
topotecan: IV, intravenous drug administration
topotecan: PO, oral drug administration
taxane derivative: AE, adverse drug reaction
taxane derivative: CT, clinical trial
taxane derivative: AD, drug administration
taxane derivative: CB, drug combination
taxane derivative: IT, drug interaction
taxane derivative: DT, drug therapy
taxane derivative: PK, pharmacokinetics
taxane derivative: PD, pharmacology
taxane derivative: IV, intravenous drug administration
taxane derivative: PO, oral drug administration
cyclosporin A: AE, adverse drug reaction
cyclosporin A: CB, drug combination
cyclosporin A: IT, drug interaction
cyclosporin A: DT, drug therapy
cyclosporin A: PD, pharmacology
fluorouracil: AE, adverse drug reaction
fluorouracil: AD, drug administration
fluorouracil: CB, drug combination
fluorouracil: DT, drug therapy
fluorouracil: IV, intravenous drug administration
fluorouracil: PO, oral drug administration
capecitabine: DT, drug therapy
capecitabine: PD, pharmacology
tegafur: DT, drug therapy
tegafur: PD, pharmacology
5 ethynyluracil: AE, adverse drug reaction
5 ethynyluracil: CT, clinical trial
5 ethynyluracil: CB, drug combination
5 ethynyluracil: IT, drug interaction
5 ethynyluracil: DT, drug therapy
5 ethynyluracil: PK, pharmacokinetics
5 ethynyluracil: PD, pharmacology
UFT: AE, adverse drug reaction
UFT: CB, drug combination
UFT: DT, drug therapy
folinic acid: AE, adverse drug reaction

folinic acid: CB, drug combination
folinic acid: DT, drug therapy
fluoropyrimidine: CB, drug combination
fluoropyrimidine: DV, drug development
fluoropyrimidine: DT, drug therapy
fluoropyrimidine: PD, pharmacology
imatinib: DT, drug therapy
imatinib: PK, pharmacokinetics
imatinib: PD, pharmacology
imatinib: PO, oral drug administration
gefitinib: AE, adverse drug reaction
gefitinib: DT, drug therapy
gefitinib: PD, pharmacology
gefitinib: PO, oral drug administration
erlotinib: AE, adverse drug reaction
erlotinib: DT, drug therapy
erlotinib: PD, pharmacology
erlotinib: PO, oral drug administration
cetuximab: AE, adverse drug reaction
cetuximab: DT, drug therapy
cetuximab: IV, intravenous drug administration
cyclophosphamide: AE, adverse drug reaction
cyclophosphamide: DT, drug therapy
cyclophosphamide: PO, oral drug administration
bms 275183: DV, drug development
bms 275183: DT, drug therapy
bms 275183: PD, pharmacology
bms 275183: PO, oral drug administration
camptothecin derivative: DV, drug development
camptothecin derivative: DT, drug therapy
camptothecin derivative: PK, pharmacokinetics
camptothecin derivative: PD, pharmacology
camptothecin derivative: PO, oral drug administration
elacridar: DV, drug development
elacridar: DT, drug therapy
elacridar: PD, pharmacology
elacridar: PO, oral drug administration
2' cyano 2' deoxy 4 n palmitoylcytarabine: DV, drug development
2' cyano 2' deoxy 4 n palmitoylcytarabine: DT, drug therapy
2' cyano 2' deoxy 4 n palmitoylcytarabine: PD, pharmacology
2' cyano 2' deoxy 4 n palmitoylcytarabine: PO, oral drug administration
antimetabolite: DV, drug development
antimetabolite: DT, drug therapy
antimetabolite: PD, pharmacology
antimetabolite: PO, oral drug administration
protein tyrosine kinase inhibitor: DV, drug development
protein tyrosine kinase inhibitor: DT, drug therapy
protein tyrosine kinase inhibitor: PD, pharmacology
protein tyrosine kinase inhibitor: PO, oral drug administration
su 006668: DV, drug development
su 006668: DT, drug therapy
su 006668: PD, pharmacology
su 006668: PO, oral drug administration
cep 701: DV, drug development
cep 701: DT, drug therapy
cep 701: PD, pharmacology
cep 701: PO, oral drug administration
3 [(3,5 dimethyl 1h pyrrol 2 yl)methylene] 1,3 dihydro 2h indol 2 one: DV, drug development
3 [(3,5 dimethyl 1h pyrrol 2 yl)methylene] 1,3 dihydro 2h indol 2 one: DT,

drug therapy
3 [(3,5 dimethyl 1h pyrrol 2 yl)methylene] 1,3 dihydro 2h indol 2 one: PD, pharmacology
3 [(3,5 dimethyl 1h pyrrol 2 yl)methylene] 1,3 dihydro 2h indol 2 one: PO, oral drug administration
tas 102: DV, drug development
tas 102: DT, drug therapy
tas 102: PD, pharmacology
tas 102: PO, oral drug administration
cp 461: DV, drug development
cp 461: DT, drug therapy
cp 461: PD, pharmacology
cp 461: PO, oral drug administration
pkc 412: DV, drug development
pkc 412: DT, drug therapy
pkc 412: PD, pharmacology
pkc 412: PO, oral drug administration
unindexed drug
unclassified drug
diflomotecan
bms 294662

RN (**topotecan**) 119413-54-6, 123948-87-8; (cyclosporin A) 59865-13-3, 63798-73-2; (fluorouracil) 51-21-8; (capecitabine) 154361-50-9; (tegafur) 17902-23-7; (5 ethynyluracil) 59989-18-3; (UFT) 74578-38-4; (folinic acid) 58-05-9, 68538-85-2; (fluoropyrimidine) 675-21-8; (imatinib) 152459-95-5, 220127-57-1; (gefitinib) 184475-35-2, 184475-55-6, 184475-56-7; (erlotinib) 183319-69-9; (cetuximab) 205923-56-4; (cyclophosphamide) 50-18-0; (elacridar) 143664-11-3; (2' cyano 2' deoxy 4 n palmitoylcytarabine) 151823-14-2; (cep 701) 111358-88-4, 156256-78-9; (3 [(3,5 dimethyl 1h pyrrol 2 yl)methylene] 1,3 dihydro 2h indol 2 one) 186610-95-7; (diflomotecan) 220997-97-7

CN Bn 80915; **Gf 120918**; Bms 275183; Cs 682; Zd 1839; Osi 774; Su 006668; Bms 294662; Su 5416; Tas 102; Cp 461; Pkc 412

L154 ANSWER 12 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2002218265 EMBASE

TI [Natural protection for the body. Drug transporters in the gastro-intestinal tract].
GENEESMIDDELTRANSPORTERS IN HET MAAGDARMKANAAL: NATUURLIJKE BESCHERMERS VAN HET LICHAAM.

AU Jorritsma A.; Schinkel A.H.; Schellens J.H.M.; Beijnen J.H.

CS Dr. J.H. Beijnen, Apotheek Slotervaartzienhuis, Antoni van Leeuwenhoekhuis, Louwesweg 6, 1066 EC Amsterdam, Netherlands

SO Pharmaceutisch Weekblad, (21 Jun 2002) 137/25 (904-910).
Refs: 25
ISSN: 0031-6911 CODEN: PHWEAW

CY Netherlands

DT Journal; (Short Survey)

FS 030 Pharmacology
037 Drug Literature Index

LA Dutch

SL English

AB Multidrug resistance research has revealed an important role for drug transporters. These transmembrane transporters also appeared to have a function under normal physiological circumstances, where they protect the body against potentially harmful substances. In the gut, some of the transporters are able to prevent the uptake of drugs, which causes a low oral bioavailability. P-glycoprotein is the most studied transporter and many P-glycoprotein substrates have low oral bioavailability. However, the

bioavailability of substrates strongly increases in P-glycoprotein-deficient mice and also when a P-glycoprotein inhibitor is co-administered with the substrate in wild type animals. Another group of drug transporters are the 'multidrug resistance-associated proteins' (MRPs). MRP(1) and MRP(2) are present under normal physiological circumstances where they have a protective function. Their influence on the oral bioavailability of substrates has not been determined yet. The 'breast cancer resistance protein' (BCRP) is a recently identified drug transporter. Like P-glycoprotein, BCRP is able to influence the intestinal uptake of drugs. There is a strong overlap between substrates of BCRP and P-glycoprotein and it is therefore difficult to determine the exact influence of BCRP on oral bioavailability. In the future, this will be possible by using recently developed BCRP-deficient mice. The various drug transporters can be important factors in the intestinal uptake of substrates. It is important to expand our knowledge about these transporters and safe inhibitors in order to improve the oral bioavailability of affected drugs.

CT Medical Descriptors:
*intestine absorption
*drug transport
protection
multidrug resistance
drug uptake
drug bioavailability
protein localization
protein binding
nonhuman
short survey
Drug Descriptors:
glycoprotein P: EC, endogenous compound
multidrug resistance protein: EC, endogenous compound
cell protein: EC, endogenous compound
breast cancer resistance protein: EC, endogenous compound
antineoplastic agent: CB, drug combination
antineoplastic agent: PK, pharmacokinetics
antineoplastic agent: PO, oral drug administration
topotecan: CB, drug combination
topotecan: PK, pharmacokinetics
topotecan: PO, oral drug administration
elacridar: CB, drug combination
elacridar: PK, pharmacokinetics
elacridar: PO, oral drug administration
unclassified drug

RN (multidrug resistance protein) 149200-37-3, 208997-77-7; (**topotecan**) 119413-54-6, 123948-87-8; (elacridar) 143664-11-3

L154 ANSWER 13 OF 25 MEDLINE on STN
AN 2002475189 MEDLINE
DN PubMed ID: 12237778
TI Induction of breast cancer resistance protein by the **camptothecin derivative** DX-8951f is associated with minor reduction of antitumour activity.
AU van Hattum A H; Hoogsteen I J; Schluper H M M; Maliepaard M; Scheffer G L; Scheper R J; Kohlhagen G; Pommier Y; Pinedo H M; Boven E
CS Department of Medical Oncology, Vrije Universiteit Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
SO British journal of cancer, (2002 Sep 9) 87 (6) 665-72.
Journal code: 0370635. ISSN: 0007-0920.
CY Scotland: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020919
Last Updated on STN: 20021026
Entered Medline: 20021024
AB DX-8951f (exatecan mesylate), a new water-soluble **derivative** of **camptothecin**, is currently being evaluated in phase II clinical trials. Resistance may be acquired when treating cancer patients with DX-8951f. Therefore, we selected a subline of the human ovarian cancer cell line A2780 for resistance against DX-8951f to investigate possible mechanisms of resistance. This DX-8951f-resistant subline, designated 2780DX8 (resistance factor=9.3), displayed a typical cross-resistance pattern including compounds, such as topotecan (resistance factor =34), SN-38 (resistance factor =47), mitoxantrone (resistance factor =59) and doxorubicin (resistance factor =2.9), which have previously been associated with the expression of breast cancer resistance protein. 2780DX8 cells did not show changes in the topoisomerase I gene, in topoisomerase I protein levels or catalytic activity. Overexpression of breast cancer resistance protein could be detected, both at the mRNA and protein level, while staining for Pgp, MRP1, or LRP was negative. GF120918, an inhibitor of breast cancer resistance protein, was able to reverse the DX-8951f-induced resistance in 2780DX8 cells. In vivo experiments in well-established 2780DX8 human tumour xenografts demonstrated that the growth inhibition induced by CPT-11 was more affected by breast cancer resistance protein expression than that of DX-8951f. These data indicate for the first time that DX-8951f is able to induce breast cancer resistance protein as a mechanism of resistance. Breast cancer resistance protein, however, results in only minor reduction of antitumour activity of DX-8951f which is an advantage over topotecan and CPT-11/SN-38.
CT Check Tags: Comparative Study; Female; Human
*ATP-Binding Cassette Transporters: ME, metabolism
Acridines: PD, pharmacology
Animals
Antigens, CD: ME, metabolism
Antineoplastic Agents, Phytogenic: AD, administration & dosage
*Antineoplastic Agents, Phytogenic: TU, therapeutic use
Breast Neoplasms: DT, drug therapy
Breast Neoplasms: ME, metabolism
Camptothecin: AD, administration & dosage
Camptothecin: AA, analogs & derivatives
*Camptothecin: TU, therapeutic use
Cell Division: DE, drug effects
Cell Division: PH, physiology
DNA Topoisomerases, Type I: AI, antagonists & inhibitors
DNA Topoisomerases, Type I: GE, genetics
DNA Topoisomerases, Type I: ME, metabolism
Drug Resistance, Neoplasm
Immunoenzyme Techniques
Isoquinolines: PD, pharmacology
*Membrane Glycoproteins
Mice
Mice, Nude
Mutation
Neoplasm Proteins: ME, metabolism
*Neoplasms, Experimental: DT, drug therapy
Neoplasms, Experimental: PA, pathology
*Ovarian Neoplasms: DT, drug therapy
P-Glycoprotein: ME, metabolism

*Tetrahydroisoquinolines
Tetrazolium Salts: DU, diagnostic use
Thiazoles: DU, diagnostic use
Tumor Cells, Cultured: CY, cytology
Tumor Cells, Cultured: DE, drug effects
RN **143664-11-3 (GF 120918)**; 147785-22-6 (CD9 antigen); 298-93-1 (thiazolyl blue); 7689-03-4 (Camptothecin)
CN 0 (ABCG2 protein, human); 0 (ATP-Binding Cassette Transporters); 0 (Acridines); 0 (Antigens, CD); 0 (Antineoplastic Agents, Phytogenic); **0 (DX 8951)**; 0 (Isoquinolines); 0 (Membrane Glycoproteins); 0 (Neoplasm Proteins); 0 (P-Glycoprotein); 0 (Tetrahydroisoquinolines); 0 (Tetrazolium Salts); 0 (Thiazoles); EC 5.99.1.2 (DNA Topoisomerases, Type I)

L154 ANSWER 14 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2003003508 EMBASE
TI Improvement of oral drug treatment by temporary inhibition of drug transporters and/or cytochrome P450 in the gastrointestinal tract and liver: An overview.
AU Kruijtzer C.M.F.; Beijnen J.H.; Schellens J.H.M.
CS Dr. J.H.M. Schellens, Netherlands Cancer Institute, Department of Medical Oncology, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands. jhm@nki.nl
SO Oncologist, (2002) 7/6 (516-530).
Refs: 172
ISSN: 1083-7159 CODEN: OCOLF6
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The oral bioavailability of many cytotoxic drugs is low and/or highly variable. This can be caused by high affinity for drug transporters and activity of metabolic enzymes in the gastrointestinal tract and liver. In this review, we will describe the main involved drug transporters and metabolic enzymes and discuss novel methods to improve oral treatment of affected substrate drugs. Results of preclinical and clinical phase I and II studies will be discussed in which affected substrate drugs, such as paclitaxel, docetaxel, and **topotecan**, are given orally in combination with an inhibitor of drug transport or drug metabolism. Future randomized studies will, hopefully, confirm that this strategy for oral treatment is at least as equally effective and safe as standard intravenous administration of these drugs.
CT Medical Descriptors:
*drug inhibition
*drug transport
gastrointestinal tract
liver
drug bioavailability
drug receptor binding
drug absorption
area under the curve
drug blood level
drug elimination
article
priority journal
Drug Descriptors:
*cytochrome P450

*cytotoxic agent: IT, drug interaction
*cytotoxic agent: PK, pharmacokinetics
*cytotoxic agent: PD, pharmacology
*cytotoxic agent: IV, intravenous drug administration
*cytotoxic agent: PO, oral drug administration
*paclitaxel: PK, pharmacokinetics
*paclitaxel: PD, pharmacology
*paclitaxel: IV, intravenous drug administration
*paclitaxel: PO, oral drug administration
*docetaxel: IT, drug interaction
*docetaxel: PK, pharmacokinetics
*docetaxel: PD, pharmacology
*docetaxel: PO, oral drug administration
***topotecan: PK, pharmacokinetics**
***topotecan: PD, pharmacology**
***topotecan: IV, intravenous drug administration**
***topotecan: PO, oral drug administration**
verapamil: PD, pharmacology
quinidine: PD, pharmacology
cyclosporin A: PD, pharmacology
elacridar: PD, pharmacology
1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol: PD, pharmacology
valspodar: PD, pharmacology
biricodar: PD, pharmacology
multidrug resistance protein
ritonavir: IT, drug interaction
irinotecan: IT, drug interaction
irinotecan: PK, pharmacokinetics
irinotecan: PD, pharmacology
ketoconazole: IT, drug interaction

RN (cytochrome P450) 9035-51-2; (paclitaxel) 33069-62-4; (docetaxel) 114977-28-5; (**topotecan**) 119413-54-6, 123948-87-8; (verapamil) 152-11-4, 52-53-9; (quinidine) 56-54-2; (cyclosporin A) 59865-13-3, 63798-73-2; (elacridar) 143664-11-3; (1 [4 (11,11 difluorodibenzo[b,e]bicyclo[5.1.0]oct 5 yl) 1 piperazinyl] 3 (5 quinolinyloxy) 2 propanol) 167465-36-3; (valspodar) 121584-18-7; (biricodar) 174254-13-8; (multidrug resistance protein) 149200-37-3, 208997-77-7; (ritonavir) 155213-67-5; (**irinotecan**) 100286-90-6; (ketoconazole) 65277-42-1

L154 ANSWER 15 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2003283112 EMBASE

TI Pharmacokinetics in cancer treatment: Clinical implications of interindividual variability and drug interactions.

AU Boven E.

CS Dr. E. Boven, Department of Medical Oncology, Vrije Universiteit Medical Centre, De Boelelaan 1117, Amsterdam, 1081 HV, Netherlands. e.boven@vumc.nl

SO American Journal of Cancer, (2002) 1/1 (33-53).
Refs: 205
ISSN: 1175-6357 CODEN: AJCMCB

CY New Zealand

DT Journal; General Review

FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LA English

SL English

AB The design of chemotherapy schedules for treatment of malignancies is based on the selection of optimal drug doses with tolerable adverse effects. Interindividual variation in absorption, distribution, metabolism and excretion may exist for a given dose, which depend on both physiological and pathological factors. These factors will be of importance for the outcome of treatment in terms of efficacy as well as toxicity. As chemotherapy usually consists of a combination of drugs, pharmacological interactions may be expected. This also holds for other drug classes, such as analgesics, antidepressants, antibiotics, that are frequently coadministered to patients receiving chemotherapy. The study of pharmacokinetics can give insight in to the extent of interindividual variability based on genetic and patient factors, as well as in the occurrence of drug interactions. Many anticancer agents need specific enzymes for their metabolism. Polymorphisms in gene expression resulting in differences in enzyme activity have been described, such as thiopurine methyltransferase for metabolism of 6-mercaptopurine, dihydropyrimidine dehydrogenase for fluorouracil and uridine diphosphate (UDP) glucuronosyl transferase 1A1 for SN-38 (the active metabolite of **irinotecan**). Cytochrome P450 isoenzymes form a very important drug-metabolizing family and CYP3A4 is responsible for the metabolism of several classes of drugs. This isoenzyme system can easily be induced or inhibited by other drugs. Interactions combining drugs requiring both CYP3A4 for metabolism and P170-glycoprotein (Pgp) for transport may result in enhanced adverse effects in patients. A well-known example is the interference of taxanes with the pharmacokinetics of anthracyclines. Patient factors, other than variable expression of drug-metabolizing enzymes, that may account for altered pharmacokinetic properties are: age, obesity, hypoalbuminemia, impaired renal or liver function. A combination of these factors may occur, especially in patients with advanced cancer. The presence of a drug interaction may be advantageous in some instances. For example, the limited oral bioavailability of paclitaxel may be improved by inhibition of Pgp-mediated drug efflux from the intestine. The same holds true for blocking the breast cancer resistance protein transporter in the intestine to enhance oral absorption of **topotecan.** It is only through prospective, preclinical and early clinical evaluation of both pharmacokinetics and pharmacodynamics, i.e. the effects of the drug on the body, that the pharmacological behavior of a particular drug can be identified. Changes in drug dose, sequence, or infusion duration, increase of the time-interval between drugs, etc., can be measures required to provide an optimal therapeutic index of combination chemotherapy for the patient with cancer.

CT Medical Descriptors:
*cancer: DR, drug resistance
*cancer: DT, drug therapy
*advanced cancer: DT, drug therapy
heredity
cancer patient
cancer chemotherapy
drug tolerability
drug choice
drug absorption
drug distribution
drug metabolism
drug excretion
protein function
gene expression
DNA polymorphism
enzyme activity
drug transport

age
obesity
hypoalbuminemia
kidney dysfunction
liver dysfunction
drug bioavailability
intestine absorption
infusion
neurotoxicity: DT, drug therapy
neurotoxicity: SI, side effect
gastrointestinal tumor: DT, drug therapy
colorectal carcinoma: DT, drug therapy
enzyme deficiency
side effect: SI, side effect
Crigler Najjar syndrome: SI, side effect
Gilbert disease: SI, side effect
diarrhea: SI, side effect
neutropenia: SI, side effect
mucosa inflammation: SI, side effect
lymphatic leukemia: DT, drug therapy
bone marrow suppression: SI, side effect
multidrug resistance
human
clinical trial
review
priority journal
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: IT, drug interaction
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: PK, pharmacokinetics
*anthracycline derivative: AE, adverse drug reaction
*anthracycline derivative: CT, clinical trial
*anthracycline derivative: IT, drug interaction
*anthracycline derivative: DT, drug therapy
*anthracycline derivative: PK, pharmacokinetics
*cyclophosphamide derivative: AE, adverse drug reaction
*cyclophosphamide derivative: CT, clinical trial
*cyclophosphamide derivative: IT, drug interaction
*cyclophosphamide derivative: DT, drug therapy
*cyclophosphamide derivative: PK, pharmacokinetics
*ifosfamide: CT, clinical trial
*ifosfamide: IT, drug interaction
*ifosfamide: DT, drug therapy
*ifosfamide: PK, pharmacokinetics
*epipodophyllotoxin derivative: CT, clinical trial
*epipodophyllotoxin derivative: IT, drug interaction
*epipodophyllotoxin derivative: DT, drug therapy
*epipodophyllotoxin derivative: PK, pharmacokinetics
*taxane derivative: CT, clinical trial
*taxane derivative: IT, drug interaction
*taxane derivative: DT, drug therapy
*taxane derivative: PK, pharmacokinetics
Vinca alkaloid: CT, clinical trial
Vinca alkaloid: IT, drug interaction
Vinca alkaloid: DT, drug therapy
Vinca alkaloid: PK, pharmacokinetics
camptothecin derivative: CT, clinical trial
camptothecin derivative: IT, drug interaction

camptothecin derivative: DT, drug therapy
camptothecin derivative: PK, pharmacokinetics
platinum derivative: CT, clinical trial
platinum derivative: IT, drug interaction
platinum derivative: DT, drug therapy
platinum derivative: PK, pharmacokinetics
gemcitabine: CT, clinical trial
gemcitabine: IT, drug interaction
gemcitabine: DT, drug therapy
gemcitabine: PK, pharmacokinetics
glycoprotein P
glycoprotein p170
verapamil: CT, clinical trial
verapamil: IT, drug interaction
verapamil: DT, drug therapy
verapamil: PK, pharmacokinetics
cyclosporin derivative: AE, adverse drug reaction
cyclosporin derivative: CT, clinical trial
cyclosporin derivative: IT, drug interaction
cyclosporin derivative: DT, drug therapy
cyclosporin derivative: PK, pharmacokinetics
analgesic agent: IT, drug interaction
antidepressant agent: IT, drug interaction
antibiotic agent: IT, drug interaction
thiopurine methyltransferase: EC, endogenous compound
cytochrome P450 isoenzyme: EC, endogenous compound
mercaptopurine: CT, clinical trial
mercaptopurine: IT, drug interaction
mercaptopurine: DT, drug therapy
mercaptopurine: PK, pharmacokinetics
dihydropyrimidine dehydrogenase: EC, endogenous compound
fluorouracil: AE, adverse drug reaction
fluorouracil: CT, clinical trial
fluorouracil: IT, drug interaction
fluorouracil: DT, drug therapy
fluorouracil: PK, pharmacokinetics
glucuronosyltransferase: EC, endogenous compound
7 ethyl 10 hydroxycamptothecin: CT, clinical trial
7 ethyl 10 hydroxycamptothecin: IT, drug interaction
7 ethyl 10 hydroxycamptothecin: DT, drug therapy
7 ethyl 10 hydroxycamptothecin: PK, pharmacokinetics
irinotecan: AE, adverse drug reaction
irinotecan: CT, clinical trial
irinotecan: IT, drug interaction
irinotecan: DT, drug therapy
irinotecan: PK, pharmacokinetics
cytochrome P450 3A4: EC, endogenous compound
paclitaxel: CT, clinical trial
paclitaxel: IT, drug interaction
paclitaxel: DT, drug therapy
paclitaxel: PK, pharmacokinetics
paclitaxel: PO, oral drug administration
carrier protein
thymidine: DT, drug therapy
unindexed drug
unclassified drug
2,4 bis(allylamino) 6 [4 [[2,2 bis(4 fluorophenyl)ethyl]amino]piperidino]
1,3,5 triazine
r 101933
elacridar

RN (ifosfamide) 3778-73-2; (gemcitabine) 103882-84-4; (verapamil) 152-11-4, 52-53-9; (thiopurine methyltransferase) 67339-09-7; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (dihydropyrimidine dehydrogenase) 9026-89-5; (fluorouracil) 51-21-8; (glucuronosyltransferase) 37329-64-9, 9030-08-4; (7 ethyl 10 hydroxycamptothecin) 86639-52-3; (**irinotecan**) 100286-90-6; (cytochrome P450 3A4) 329736-03-0; (paclitaxel) 33069-62-4; (carrier protein) 80700-39-6; (thymidine) 50-89-5; (2,4 bis(allylamino) 6 [4 [[2,2 bis(4 fluorophenyl)ethyl]amino]piperidino] 1,3,5 triazine) 140945-01-3; (elacridar) 143664-11-3
CN Sn 38; S 9788; R 101933; **Gf 120918**

L154 ANSWER 16 OF 25 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2002013681 EMBASE
TI The use of oral cytotoxic and cytostatic drugs in cancer treatment.
AU Sparreboom A.; De Jonge M.J.A.; Verweij J.
CS A. Sparreboom, Department of Medical Oncology, Rotterdam Cancer Inst. (D.d.H.K.), University Hospital Rotterdam, 3075 EA Rotterdam, Netherlands. sparreboom@onch.azr.nl
SO European Journal of Cancer, (2002) 38/1 (18-22).
Refs: 28
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(01)00322-7
CY United Kingdom
DT Journal; General Review
FS 010 Obstetrics and Gynecology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Although with a few exceptions, most new anticancer agents are initially developed for intravenous use, oral treatment with anticancer agents is, if feasible, to be preferred, as this route of administration is convenient to patients, reduces administration costs and facilitates the use of more chronic treatment regimens. Recent studies have identified various physiological barriers limiting the oral absorption of anticancer drugs. Presently, several strategies are explored to alter the low and variable oral bioavailability of several important anticancer agents by taking advantage of an intentional interaction between anticancer agents and drugs that modulate active intestinal drug transporters or (intestinal) enzymes. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.
CT Medical Descriptors:
*ovary cancer: DT, drug therapy
*lung small cell cancer: DT, drug therapy
drug use
cancer therapy
cost effectiveness analysis
long term care
physiology
drug absorption
drug bioavailability
protein expression
area under the curve
dose response
drug potentiation
drug efficacy

drug safety
drug tolerability
patient compliance
outpatient department
blood toxicity: SI, side effect
human
nonhuman
Hypericum perforatum
review
priority journal
Drug Descriptors:
*cytotoxic agent: AE, adverse drug reaction
*cytotoxic agent: AD, drug administration
*cytotoxic agent: CB, drug combination
*cytotoxic agent: IT, drug interaction
*cytotoxic agent: DT, drug therapy
*cytotoxic agent: PK, pharmacokinetics
*cytotoxic agent: IV, intravenous drug administration
*cytotoxic agent: PO, oral drug administration
*cytostatic agent: AE, adverse drug reaction
*cytostatic agent: AD, drug administration
*cytostatic agent: CB, drug combination
*cytostatic agent: IT, drug interaction
*cytostatic agent: DT, drug therapy
*cytostatic agent: PK, pharmacokinetics
*cytostatic agent: IV, intravenous drug administration
*cytostatic agent: PO, oral drug administration
topotecan: AE, adverse drug reaction
topotecan: AD, drug administration
topotecan: DT, drug therapy
topotecan: PK, pharmacokinetics
topotecan: IV, intravenous drug administration
topotecan: PO, oral drug administration
intestine enzyme: EC, endogenous compound
glycoprotein P: EC, endogenous compound
protein: EC, endogenous compound
paclitaxel: AD, drug administration
paclitaxel: PK, pharmacokinetics
paclitaxel: PO, oral drug administration
taxane derivative: AD, drug administration
taxane derivative: CB, drug combination
taxane derivative: PK, pharmacokinetics
taxane derivative: PO, oral drug administration
cyclosporin A: AD, drug administration
cyclosporin A: CB, drug combination
cyclosporin A: IT, drug interaction
cyclosporin A: PK, pharmacokinetics
cyclosporin A: PO, oral drug administration
elacridar: AD, drug administration
elacridar: CB, drug combination
elacridar: PK, pharmacokinetics
elacridar: PO, oral drug administration
rifampicin: IT, drug interaction
digoxin: IT, drug interaction
7 ethyl 10 hydroxycamptothecin: IT, drug interaction
indinavir: IT, drug interaction
RN (**topotecan**) 119413-54-6, 123948-87-8; (protein) 67254-75-5; (paclitaxel) 33069-62-4; (cyclosporin A) 59865-13-3, 63798-73-2; (elacridar) 143664-11-3; (rifampicin) 13292-46-1; (digoxin) 20830-75-5, 57285-89-9; (7 ethyl 10 hydroxycamptothecin) 86639-52-3; (indinavir)

150378-17-9, 157810-81-6, 180683-37-8
CN Sn 38; **Gf 120918**

L154 ANSWER 17 OF 25 ZCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
AN 2000:824069 ZCAPLUS
DN 134:9341
ED Entered STN: 24 Nov 2000
TI A method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compositions for oral delivery of drugs
IN Schellens, Johannes Henricus Matthias; Schinkel, Alfred Hermanus
PA Het Nederlands Kanker Instituut, Neth.
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 63-5 (Pharmaceuticals)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2000069390	A2	20001123	WO 2000-NL331	20000517	<--
	WO 2000069390	A3	20011213			
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	AU 2000049552	A5	20010205	AU 2000-49552	20000517	<--
	EP 1189637	A2	20020327	EP 2000-931720	20000517	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
	US 2002128282	A1	20020912	US 2001-988285	20011119	<--
PRAI	NL 1999-1012066	A	19990517	<--		
	NL 1999-1012481	A	19990630	<--		
	WO 2000-NL331	W	20000517			

AB A method for increasing the systemic exposure of cells selected from tumor cells and normal cells to an orally administered pharmaceutically active compound, wherein a bioenhancer comprising an inhibitor of breast cancer resistance protein (BCRP)-mediated and/or related drug transport is orally administered concomitantly with said orally administered pharmaceutically active compound, and in which method the inhibitor is administered simultaneously with the pharmaceutical compound Mice were given oral GF120918 (50 mg/kg) 15 min before oral dose of 1 mg/kg topotecan. A profound increased systemic exposure to oral topotecan was observed The increase in the AUC was approx. 6 fold.
ST oral pharmaceutical bioavailability permeation enhancer; breast cancer resistance protein inhibitor pharmaceutical
IT Antitumor agents
(mammary gland; method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)
IT Antitumor agents
Digestive tract
Drug bioavailability
Permeation enhancers

(method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT Mycotoxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT Mammary gland
(neoplasm, inhibitors; method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT Drug delivery systems
(oral; method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT **180422-22-4**, XR 9051
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(XR 9051; method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT **206873-63-4**, XR 9576
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(XR 9576; method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

IT 84-65-1D, Anthraquinone, derivs. 253-82-7D, Quinazoline, derivs. **7689-03-4D**, Camptothecin, **derivs.** 19216-56-9, Prazosin 65271-80-9, Mitoxantrone 86639-52-3, Sn38 **91421-42-0**, 9-Nitrocamptothecin **91421-43-1**, 9-Aminocamptothecin **100286-90-6**, Cpt11 118974-02-0, Fumitremorgin c **123948-87-8**, Topotecan. **143664-11-3**, GF120918 **149882-10-0**, Gg211 **169869-90-3**, Dx8951f **203923-89-1**, Bnp 1350
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of improving bioavailability of orally administered drugs, screening for enhancers of such bioavailability and novel pharmaceutical compns. for oral delivery of drugs)

L154 ANSWER 18 OF 25 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 3
AN 2000:511112 BIOSIS
DN PREV200000511112
TI Role of breast cancer resistance protein in the bioavailability and fetal penetration of **topotecan.**
AU Jonker, Johan W.; Smit, Johan W.; Brinkhuis, Remco F.; Maliepaard, Marc; Beijnen, Jos H.; Schellens, Jan H. M.; Schinkel, Alfred H. [Reprint author]
CS Division of Experimental Therapy, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, Netherlands
SO Journal of the National Cancer Institute (Bethesda), (October 18, 2000) Vol. 92, No. 20, pp. 1651-1656. print.

CODEN: JNCIEQ. ISSN: 0027-8874.
DT Article
LA English
ED Entered STN: 22 Nov 2000
Last Updated on STN: 11 Jan 2002
AB Background and Methods: Breast cancer resistance protein (BCRP/MXR/ABCP) is a multidrug-resistance protein that is a member of the adenosine triphosphate-binding cassette family of drug transporters. BCRP can render tumor cells resistant to the anticancer drugs **topotecan**, mitoxantrone, doxorubicin, and daunorubicin. To investigate the physiologic role of BCRP, we used polarized mammalian cell lines to determine the direction of BCRP drug transport. We also used the BCRP inhibitor GF120918 to assess the role of BCRP in protecting mice against xenobiotic drugs. Bcrp1, the murine homologue of BCRP, was expressed in the polarized mammalian cell lines LLC-PK1 and MDCK-II, and the direction of Bcrp1-mediated transport of **topotecan** and mitoxantrone was determined. To avoid the confounding drug transport provided by P-glycoprotein (P-gp), the roles of Bcrp1 in the bioavailability of **topotecan** and the effect of GF120918 were studied in both wild-type and P-gp-deficient mice and their fetuses. Results: Bcrp1 mediated apically directed transport of drugs in polarized cell lines. When both **topotecan** and GF120918 were administered orally, the bioavailability (i.e., the extent to which a drug becomes available to a target tissue after administration) of **topotecan** in plasma was dramatically increased in P-gp-deficient mice (greater than sixfold) and wild-type mice (greater than ninefold), compared with the control (i.e., vehicle-treated) mice. Furthermore, treatment with GF120918 decreased plasma clearance and hepatobiliary excretion of **topotecan** and increased (re-)uptake by the small intestine. In pregnant GF120918-treated, P-gp-deficient mice, relative fetal penetration of **topotecan** was twofold higher than that in pregnant vehicle-treated mice, suggesting a function for BCRP in the maternal-fetal barrier of the placenta. Conclusions: Bcrp1 mediates apically directed drug transport, appears to reduce drug bioavailability, and protects fetuses against drugs. We propose that strategic application of BCRP inhibitors may thus lead to more effective oral chemotherapy with **topotecan** or other BCRP substrate drugs.
CC Pharmacology - General 22002
Biochemistry studies - General 10060
Pathology - Therapy 12512
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Development and Embryology - General and descriptive 25502
IT Major Concepts
Pharmacology; Tumor Biology
IT Chemicals & Biochemicals
GF-120918: antineoplastic-drug, breast cancer resistance protein inhibitor, drug resistance reversing agent; breast cancer resistance protein: fetal **topotecan** penetration role, **topotecan** bioavailability role; **topotecan** [Hyacinthin]: antineoplastic-drug, bioavailability, fetal penetration, tumor resistance
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model, female, fetus
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,

Rodents, Vertebrates
RN 143664-11-3 (**GF-120918**)
123948-87-8 (**topotecan**)
123948-87-8 (Hyacinthin)
38890-82-3 (HYACINTHIN)

L154 ANSWER 19 OF 25 ZCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:795688 ZCAPLUS
DN 132:35333
ED Entered STN: 17 Dec 1999
TI Multibinding inhibitors of topoisomerase
IN Linsell, Martin S.; Meier-Davis, Susan; Griffin, John H.
PA Advanced Medicine, Inc., USA
SO PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-00
ICS A61K039-00; A61K039-44; A61K039-395; A61K051-00; C07K002-00; C07K004-00; G01N033-53; G01N033-543; G01N033-566; C07G011-00
CC 21-2 (General Organic Chemistry)
Section cross-reference(s): 1, 63
FAN.CNT 31

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9964054	A1	19991216	WO 1999-US12908	19990608	<--
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	US 6288234	B1	20010911	US 1999-325662	19990604	<--
	CA 2321166	AA	19991216	CA 1999-2321166	19990608	<--
	AU 9946771	A1	19991230	AU 1999-46771	19990608	<--
	EP 1085891	A1	20010328	EP 1999-930179	19990608	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	SG 80631	A1	20010522	SG 1999-2719	19990608	<--
	SG 90053	A1	20020723	SG 1999-2944	19990608	<--
	US 6566509	B1	20030520	US 1999-327899	19990608	<--
	ZA 2000004086	A	20010810	ZA 2000-4086	20000810	<--
	ZA 2000004558	A	20011130	ZA 2000-4558	20000831	<--
	ZA 2000004559	A	20020402	ZA 2000-4559	20000831	<--
	US 2002028943	A1	20020307	US 2001-760827	20010117	<--
	US 2004023290	A1	20040205	US 2002-161279	20020603	<--
	US 2003176670	A1	20030918	US 2002-330381	20021227	<--
PRAI	US 1998-88448P	P	19980608	<--		
	US 1998-93072P	P	19980716	<--		
	US 1999-325662	A3	19990604	<--		
	US 1999-327899	A1	19990608	<--		
	US 1999-328071	B1	19990608	<--		
	WO 1999-US12908	W	19990608	<--		
	US 2000-502938	A1	20000211			

AB Novel topoisomerase inhibitors that act as multibinding agents, LpXq [where L = a ligand capable of binding to topoisomerase; X = a linker; p = 2-10; q = 1-20; the distance between ligands 2-50 Å], are disclosed.

Combinatorial arrays, methods of synthesis, and methods of assaying the dimeric and multimeric compds. are also embodied by the invention. A number of divalent prophetic examples, derived from substituted fused ring heterocyclic ligands and difunctional linkers, are given. Compds. of this invention are useful in the treatment and prevention of cancer and microbial infections (no data). The multibinding compds. provide greater biol. and/or therapeutic effects than the aggregate of the unlinked ligands due to their multibinding properties (no data). Ligands may include A-62176, A-74932, acridine carboxamides, actinomycin D, AD-312, AD-347, AHMA, AMP-53, amrubicin, amsacrine, anthracyclines, asulacrine, azonafide, azatoxin, BBR-2778, BMY-43748, BO-2367, bromodeoxyuridine, C-1310, C-1311, CC-131, CJ-12373, CI-937, CI-920 (fostriecin), CP-115953, camptothecin, daunorubicin, doxorubicin, DuP 937 (losoxathrone), DuP 941, elinafide, ellipticine-estradiol (conjugates), elsamitrucin, ER-37328, etoposide, fleroxacin, GI-149893, GL-331, GR-1222222X, ICRF-154, ICRF-193, idarubicin, iododoxorubicin, IST-622, KRQ- 10018, intoplicine, lomefloxacin, losoxantrone, m-AMSA, merbarone, meraboin, mitonafide, mitoxantrone, morindone, NCA-0465, NK-109, NK-611, NSC-655649, NSC-665517, NSC-675967, pazelliptine, pazufloxacin, PD-131112, piroxantrone, pyridobenzophenoxazine, S-16020-2, saintopin, sitafloxacin hydrate, SN-22995, sobuzoxane, SR-103, TAS-103, teloxantrone, teniposide, TLC-D-99, top-53, topotecan, tosufloxacin, TRK-710, trovafloxacin, UCE-6, VM-26, VP-16, W5R, WIN-33377, WIN-58161, WIN-645593, WQ-2743, WQ-3034, WR-63320, XR-5942, XR-5000, and 773U82.

ST dimeric multimeric multibinding topoisomerase inhibitor prepn; combinatorial array multibinding topoisomerase inhibitor; anticancer multibinding topoisomerase inhibitor prepn; antimicrobial multibinding topoisomerase inhibitor prepn

IT Structure-activity relationship
(ligand-binding; preparation of multibinding inhibitors of topoisomerase as anticancer and antimicrobial agents)

IT Antimicrobial agents
Antitumor agents
Combinatorial library
Drug delivery systems
Drug screening
(preparation of multibinding inhibitors of topoisomerase as anticancer and antimicrobial agents)

IT Anthracyclines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of multibinding inhibitors of topoisomerase as anticancer and antimicrobial agents)

IT 80449-01-0
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of multibinding inhibitors of topoisomerase as anticancer and antimicrobial agents)

IT 50-28-2DP, Estradiol, dimeric and multimeric derivs. of 50-76-0DP, Actinomycin D, dimeric and multimeric derivs. of 59-14-3DP, Bromodeoxyuridine, dimeric and multimeric derivs. of **260-94-6DP**, Acridine, dimeric and multimeric **derivs.** of 478-29-5DP, Morindone, dimeric and multimeric derivs. of 519-23-3DP, Ellipticine, dimeric and multimeric derivs. of 1506-47-4DP, ICRF-154, dimeric and multimeric derivs. of **7689-03-4DP**, Camptothecin, dimeric and multimeric **derivs.** of 20830-81-3DP, Daunorubicin, dimeric and multimeric derivs. of 21416-88-6DP, ICRF-193, dimeric and multimeric derivs. of 23214-92-8DP, Doxorubicin, dimeric and multimeric derivs. of 29767-20-2DP, Teniposide, dimeric and multimeric derivs. of

33419-42-0DP, Etoposide, dimeric and multimeric derivs. of 51264-14-3DP, Amsacrine, dimeric and multimeric derivs. of 54824-17-8DP, Mitonafide, dimeric and multimeric derivs. of 58957-92-9DP, Idarubicin, dimeric and multimeric derivs. of 65222-35-7DP, Pazelliptine, dimeric and multimeric derivs. of 65271-80-9DP, Mitoxantrone, dimeric and multimeric derivs. of 79660-72-3DP, Fleroxacin, dimeric and multimeric derivs. of 83997-75-5DP, Iododoxorubicin, dimeric and multimeric derivs. of 87810-56-8DP, Fostriecin, dimeric and multimeric derivs. of 88303-60-0DP, Losoxantrone, dimeric and multimeric derivs. of 88303-61-1DP, DUP 941, dimeric and multimeric derivs. of 89458-99-1DP, SN 22995, dimeric and multimeric derivs. of 91441-23-5DP, Piroxantrone, dimeric and multimeric derivs. of 91441-48-4DP, CI-937, dimeric and multimeric derivs. of 96404-52-3DP, 773U82, dimeric and multimeric derivs. of 97068-30-9DP, Elsamitrucin, dimeric and multimeric derivs. of 97534-21-9DP, Merbarone, dimeric and multimeric derivs. of 98079-51-7DP, Lomefloxacin, dimeric and multimeric derivs. of 98631-95-9DP, Sobuzoxane, dimeric and multimeric derivs. of 100490-36-6DP, Tosufloxacin, dimeric and multimeric derivs. of 105760-98-3DP, NK-611, dimeric and multimeric derivs. of 110267-81-7DP, Amrubicin, dimeric and multimeric derivs. of 111783-54-1DP, A-62176, dimeric and multimeric derivs. of 122033-48-1DP, WIN-58161, dimeric and multimeric derivs. of 122536-20-3DP, PD 131112, dimeric and multimeric derivs. of 123830-79-5DP, DuP 937, dimeric and multimeric derivs. of **123948-87-8DP**, Topotecan, dimeric and multimeric derivs. of 125974-72-3DP, Intoplicine, dimeric and multimeric derivs. of 127045-41-4DP, Pazufloxacin, dimeric and multimeric derivs. of 127254-12-0DP, Sitafloxacin, dimeric and multimeric derivs. of 127882-73-9DP, GL-331, dimeric and multimeric derivs. of 128201-92-3DP, IST 622, dimeric and multimeric derivs. of 128420-31-5DP, AD-312, dimeric and multimeric derivs. of 128455-95-8DP, dimeric and multimeric derivs. of 128524-35-6DP, AD 347, dimeric and multimeric derivs. of 129564-92-7DP, Azatoxin, dimeric and multimeric derivs. of 131190-63-1DP, Saintopin, dimeric and multimeric derivs. of 132195-65-4DP, BMY-43748, dimeric and multimeric derivs. of 136440-70-5DP, CP-115953, dimeric and multimeric derivs. of 138154-39-9DP, C-1311, dimeric and multimeric derivs. of 138154-40-2DP, C-1310, dimeric and multimeric derivs. of 140917-67-5DP, Azonafide, dimeric and multimeric derivs. of 143201-31-4DP, NK-109, dimeric and multimeric derivs. of 144675-97-8DP, BBR-2778, dimeric and multimeric derivs. of 145902-76-7DP, dimeric and multimeric derivs. of 146537-07-7DP, WIN-33377, dimeric and multimeric derivs. of 147059-72-1DP, Trovafloxacin, dimeric and multimeric derivs. of 148201-60-9DP, A-74932, dimeric and multimeric derivs. of 148262-19-5DP, Top-53, dimeric and multimeric derivs. of 149809-18-7DP, GI-149893, dimeric and multimeric derivs. of 150829-94-0DP, UCE-6, dimeric and multimeric derivs. of 154310-42-6DP, dimeric and multimeric derivs. of 156340-22-6DP, CJ 12373, dimeric and multimeric derivs. of 162706-37-8DP, Elinafide, dimeric and multimeric derivs. of 172889-50-8DP, NSC 665517, dimeric and multimeric derivs. of 174634-09-4DP, TAS-103, dimeric and multimeric derivs. of 178169-99-8DP, S-16020-2, dimeric and multimeric derivs. of 180981-08-2DP, TRK 710, dimeric and multimeric derivs. of 213185-01-4DP, SR-103, dimeric and multimeric derivs. of

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of multibinding inhibitors of topoisomerase as anticancer and antimicrobial agents)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Brown; Antibiotic and Chemotherapy 7th Ed 1997, P419 ZCAPLUS
(2) Ehrhardt; Antimicrobial Agents and Chemotherapy 1997, V41(11), P2570 ZCAPLUS
(3) Fan; J Med Chem 1995, V38(3), P408 ZCAPLUS
(4) NEORX Corporation; WO 9205802 A1 1992 ZCAPLUS
(5) Shuker; Science 1996, V274, P1531 ZCAPLUS

L154 ANSWER 20 OF 25 ZCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:78980 ZCAPLUS
DN 128:254161
ED Entered STN: 11 Feb 1998
TI A general pattern for substrate recognition by P-glycoprotein
AU Seelig, Anna
CS Department of Biophysical Chemistry, Biocenter of the University of Basel, Basel, CH-4056, Switz.
SO European Journal of Biochemistry (**1998**), 251(1/2), 252-261
CODEN: EJBCAI; ISSN: 0014-2956
PB Springer-Verlag
DT Journal
LA English
CC 6-1 (General Biochemistry)
AB P-glycoprotein actively transports a wide variety of chemical diverse compds. out of the cell. Based on a comparison of a hundred compds. previously tested as P-glycoprotein substrates, we suggest that a set of well-defined structural elements is required for an interaction with P-glycoprotein. The recognition elements are formed by two (type I unit) or three electron donor groups (type II unit) with a fixed spatial separation Type I units consist of two electron donor groups with a spatial separation of 2.5±0.3 Å. Type II units contain either two electron donor groups with a spatial separation of 4.6±0.6 Å or three electron donor groups with a spatial separation of the outer two groups of 4.6±0.6 Å. All mols. that contain at least one type I or one type II unit are predicted to be P-glycoprotein substrates. The binding to P-glycoprotein increases with the strength and the number of electron donor or hydrogen bonding acceptor groups forming the type I and type II units. Correspondingly, a high percentage of amino acids with hydrogen bonding donor side chains is found in the transmembrane sequences of P-glycoprotein relevant for substrate interaction. Mols. that minimally contain one type II unit are predicted to be inducers of P-glycoprotein over-expression.
ST P glycoprotein substrate inducer structure activity
IT Structure-activity relationship
(P-glycoprotein substrate and inducer; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)
IT Hormones, microbial
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(a-factor, substrate; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)
IT Hydrogen bond
(acceptor group, in P-glycoprotein; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)
IT Biological transport
(by P-glycoprotein; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)
IT Conformation
(of electron donor groups in substrates; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)
IT Electron donors
(spatial separation in P-glycoprotein; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT 50-53-3, Chlorpromazine, biological studies 52-86-8, Haloperidol 58-40-2, Promazine 59-05-2, Methotrexate 69-05-6, Quinacrine dihydrochloride 390-64-7, Prenylamine 569-61-9, Pararosaniline 1622-62-4, Flunitrazepam 5786-21-0, Clozapine 15663-27-1, Cisplatin 154531-78-9, CP 117227
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(borderline substrate; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT 50-06-6, Phenobarbital, biological studies 50-55-5, Reserpine 50-76-0, Actinomycin D 53-79-2, Puromycin 57-22-7, Vincristine 64-86-8, Colchicine 114-07-8, Erythromycin 120-58-1, Isosafrole 865-21-4, Vinblastine 13292-46-1, Rifampicin 20830-81-3, Daunorubicin 21829-25-4, Nifedipine 23214-92-8, Doxorubicin 23593-75-1, Clotrimazole 33069-62-4, Taxol 33419-42-0, Etoposide 59467-70-8, Midazolam 152044-53-6, Epothilone A
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(inducer; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT 51-43-4, Epinephrine 72-57-1, Trypan blue 83-60-3, Reserpic acid 4602-84-0, Farnesol 44641-43-2, Cysteine methylester 68000-92-0, Farnesylcysteine 75621-03-3, Chaps
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(non-substrate; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT 7727-37-9, Nitrogen, biological studies 7782-44-7, Oxygen, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(occurrence in substrates; substrate structural patterns for recognition by and induction of over-expression of P-glycoprotein)

IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 50-52-2, Thioridazine 52-39-1, Aldosterone 52-53-9, Verapamil 56-54-2, Quinidine 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-83-0, Progesterone, biological studies 58-32-2, Dipyridamole 58-39-9, Perphenazine 69-23-8, Fluphenazine 85-79-0, Dibucaine 117-89-5, Trifluoperazine 135-67-1, Phenoxazine 146-48-5, Yohimbine 146-54-3, Triflupromazine 481-49-2, Cepharanthine 483-18-1, Emetine 485-71-2, Cinchonidine 749-02-0, Spiperone 1095-90-5, Methadone hydrochloride 1951-25-3, Amiodarone 2001-95-8, Valinomycin 2182-14-1, Vindoline 2468-21-5, Catharanthine 2751-90-8, Tetraphenylphosphonium bromide 2814-89-3 2901-66-8, Methylreserpate 9002-93-1, Triton X-100 10540-29-1, Tamoxifen 16662-47-8, Gallopamil 17090-79-8, Monensin 19216-56-9, Prazosin 20290-10-2, Morphine 6-glucuronide 20830-75-5, Digoxin 25953-19-9, Cefazolin 42399-41-7, Diltiazem 50679-08-8, Terfenadine 53179-11-6, Loperamide 53772-82-0, cis-Flupenthixol 55985-32-5, Nicardipine 57808-66-9, Domperidone 59865-13-3, Cyclosporin A 62669-70-9, Rhodamine 123 62893-19-0, Cefoperazone 64706-54-3, Bepridil 65271-80-9, Mitoxantrone 69712-56-7, Cefotetan 70288-86-7, Ivermectin 78186-34-2, Bisantrene 90523-31-2, Azidopine 99614-02-5, Ondansetron 104845-40-1, SDB-ethylenediamine 104987-11-3, FK 506

120054-86-6, Dexniguldipine 121584-18-7, SDZ PSC 833 **123948-87-8**
, Topotecan 130062-64-5 137694-16-7, BIBW22BS 140945-01-3, S 9788
142716-85-6, CP 100356 **143664-11-3**, GF 120918
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP
(Properties); BIOL (Biological study); PROC (Process)
(substrate; substrate structural patterns for recognition by and
induction of over-expression of P-glycoprotein)

RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L154 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:517625 BIOSIS
DN PREV199799816828
TI Cellular responses to methyl-N-(4-(9-acridinylamino)-2-methoxyphenyl)carbamate hydrochloride, an analogue of amsacrine active against non-proliferating cells.
AU Moreland, N.; Finlay, G. J.; Dragunow, M.; Holdaway, K. M.; Baguley, B. C. [Reprint author]
CS Cancer Research Lab., Univ. Auckland Sch. Med., Private Bag 92019, Auckland 1000, New Zealand
SO European Journal of Cancer, (1997) Vol. 33, No. 10, pp. 1668-1676. CODEN: EJCAEL. ISSN: 0959-8049.
DT Article
LA English
ED Entered STN: 10 Dec 1997
Last Updated on STN: 10 Dec 1997
AB The **acridine derivative** m-AMCA (methyl-N-(4-(9-acridinylamino)-2-methoxyphenyl)carbamate hydrochloride), a carbamate analogue of the toposiomerase II poison amsacrine, is distinguished by its high cytotoxicity against non-cycling tumour cells. We compared the response of cultured Lewis lung carcinoma cells to b-AMCA, amsacrine and the topoisomerase I poison camptothecin. The DNA polymerase inhibitor aphidicolin reversed the cytotoxicity of camptothecin fully, that of amsacrine partially, and that of m-AMCA minimally. The ability of m-AMCA to induce the enzyme poly(ADP-ribose)polymerase (PARP) was markedly lower than that of camptothecin or amsacrine. Cell cycle responses to m-AMCA and amsacrine were similar, with slowing of progress through S-phase and arrest in G-2-phase. These cell cycle changes were also observed when plateau phase cultures were exposed to drug for 1 h, washed free of drug and cultured in fresh medium, with m-AMCA having a more pronounced effect than amsacrine and camptothecin having no effect. We also examined the role of p53 protein in the response using cultured human H460 cells. Both mAMCA and amsacrine induced p53 protein expression in proliferating but not in non-proliferating H460 cells, and induced p21-WAF1 regardless of proliferation status. Both induced G-1-phase cell cycle arrest. It is suggested that two cytotoxicity mechanisms can be distinguished using these drugs. The first is specific for S-phase cells, is reversed by aphidicolin and induces PARP activity. The second is cell cycle non-specific, does not induce PARP and is unaffected by aphidicolin. Camptothecin activates only the first, m-AMCA primarily the second and amsacrine activates both.
CC Cytology - Animal 02506

Cytology - Human 02508
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Therapy 12512
Respiratory system - Pathology 16006
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Respiratory system 22030
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences); Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
AMSACRINE; TOPOISOMERASE II; **CAMPTOTHECIN**; POLY-(ADP-RIBOSE) POLYMERASE

IT Miscellaneous Descriptors
AMSACRINE; AMSACRINE ANALOGUE; ANTINEOPLASTIC-DRUG; CAMPTOTHECIN; DRUG TREATMENT; DRUG-INDUCED ACTIVATION; H-460 CELL LINE; HUMAN LUNG CANCER CELL LINE; IN-VITRO MODEL SYSTEM; LLTC CELL LINE; METHYL-N-(4-(9-ACRIDINYLAMINO)-2-METHOXYPHENYL)CARBAMATE HYDROCHLORIDE; MOUSE LEWIS LUNG CARCINOMA CELL LINE; PHARMACOLOGY; POLY-(ADP-RIBOSE) POLYMERASE; TOPOISOMERASE I POISON; TOPOISOMERASE II POISON; TUMOR BIOLOGY

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hominidae
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 51264-14-3 (AMSACRINE)
142805-56-9 (TOPOISOMERASE II)
7689-03-4 (CAMPTOTHECIN)
9055-67-8 (POLY-(ADP-RIBOSE) POLYMERASE)

L154 ANSWER 22 OF 25 ZCAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:741460 ZCAPLUS
DN 126:84167
ED Entered STN: 18 Dec 1996
TI Selective induction of apoptosis in Hep 3B cells by topoisomerase I inhibitors: evidence for protease-dependent pathway that does not activate cysteine protease P32
AU Adjei, Philip N.; Kaufmann, Scott H.; Leung, Wai-Yee; Mao, Fei; Gores, Gregory J.
CS Div. Gastrointestinal Int. Med., Mayo Clinic Found., Rochester, MN, 55905, USA
SO Journal of Clinical Investigation (**1996**), 98(11), 2588-2596
CODEN: JCINAO; ISSN: 0021-9738

PB Rockefeller University Press
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Progress in the treatment of hepatocellular carcinoma (HCC), a common tumor worldwide, has been disappointing. Inhibitors of topoisomerases are being widely studied as potential inducers of tumor cell apoptosis. The authors aims were to determine whether topoisomerase-directed drugs would induce apoptosis in a human HCC cell line (Hep 3B) and, if so, to investigate the mechanism. The topoisomerase I poison camptothecin (CPT) induced apoptosis of Hep 3B cells in a time- and concentration-dependent manner.

In contrast, the topoisomerase II poison etoposide failed to induce apoptosis despite the apparent stabilization of topoisomerase II-DNA complexes. Unexpectedly, CPT-induced apoptosis in this cell type occurred without any detectable cleavage of poly(ADP-ribose) polymerase or lamin B, polypeptides that are commonly cleaved in other cell types undergoing apoptosis. Likewise, Hep 3B cell apoptosis occurred without a detectable increase in interleukin-1β-converting enzyme (ICE)-like or cysteine protease P32 (CPP32)-like protease activity. In contrast, trypsin-like protease activity (cleavage of Boc-Val-Leu-Lys-chloromethylaminocoumarin in situ) increased threefold in cells treated with CPT but not etoposide. Tosyl-lysyl chloromethyl ketone inhibited the trypsin-like protease activity and diminished CPT-induced apoptosis. These data demonstrate that (a) apoptosis is induced in Hep 3B cells after stabilization of topoisomerase I-DNA complexes but not after stabilization of topoisomerase II-DNA complexes as measured by alkaline filter elution; (b) Hep 3B cell apoptosis occurs without activation of ICE-like and CPP32-like protease activity; and (c) a trypsin-like protease activity appears to contribute to apoptosis in this cell type.

ST apoptosis hepatocellular carcinoma topoisomerase inhibitor protease

IT Liver, neoplasm
(hepatoma, inhibitors; selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

IT Antitumor agents
(hepatoma; selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

IT Apoptosis
(selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

IT 143180-75-0, DNA topoisomerase I
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(inhibitors; selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

IT **260-94-6D**, Acridine, pyrazolo-fused **derivative** 7689-03-4, Camptothecin 33419-42-0, Etoposide 86639-52-3, SN-38 **123948-87-8**, Topotecan
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for

protease-dependent pathway that does not activate cysteine protease P32)

IT 122191-40-6, Interleukin-1β-converting enzyme 169592-57-8, CPP32 proteinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

IT 37259-58-8, Serine proteinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(trypsin-like; selective induction of apoptosis in human hepatocellular carcinoma Hep 3B cells by topoisomerase I inhibitors and evidence for protease-dependent pathway that does not activate cysteine protease P32)

L154 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1996:113207 BIOSIS
DN PREV199698685342
TI Interaction of cytostatics and chemosensitizers with the dexniguldipine binding site on P-glycoprotein.
AU Boer, Rainer [Reprint author]; Ulrich, Wolf-Ruediger; Haas, Sabine; Borchers, Christoph; Gekeler, Volker; Boss, Hildegaard; Przybylski, Michael; Schoedl, Angelika
CS Byk Gulden, Byk Gulden-Str. 2, D-78467 Konstanz, Germany
SO European Journal of Pharmacology, (1996) Vol. 295, No. 2-3, pp. 253-260. CODEN: EJPHAZ. ISSN: 0014-2999.
DT Article
LA English
ED Entered STN: 12 Mar 1996
Last Updated on STN: 13 Mar 1996
AB The interaction of cytostatics and chemosensitizers with the dexniguldipine binding site of P-glycoprotein was investigated in photoaffinity labeling experiments. A tritiated azidoderivative of the chemosensitizer dexniguldipine with dihydropyridine structure, (3H)B9209-005, was used to irreversibly label P-glycoprotein. The apparent affinity of cytostatics and chemosensitizers to this binding site was estimated from labeling experiments in the presence of increasing concentrations of compounds. From the cytostatics tested, the vinca alkaloids and taxol showed the highest affinity, anthracyclins possessed moderate affinity while methotrexate, ara C and camptothecin, cytostatics not involved in P-glycoprotein-mediated multidrug resistance, were almost inactive. The chemosensitizers **GF 120918**, cyclosporin A and SDZ PSC-833 inhibited photoincorporation with the highest potency. Steep dose-inhibition curves were obtained with the cyclic peptides and S9788, indicating that these compounds may bind allosterically to a separate binding site. Compounds with dihydropyridine structure with or without chemosensitizing potency were also tested and some structure-activity relationships could be derived from the data. Our data show that inhibition of photoaffinity labeling by (3H)B9209-005 is a valuable and reliable system for measuring the interaction with and potency of chemosensitizing compounds at P-glycoprotein. Furthermore, data obtained in this test system are well suited to investigate structure-activity relationships for chemosensitizers at P-glycoprotein. In addition cytostatics underlying P-glycoprotein-mediated multidrug resistance can be identified.
CC Cytology - Human 02508
Biochemistry studies - General 10060

Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Biophysics - Membrane phenomena 10508
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Muscle system 22022
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Membranes (Cell Biology); Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
METHOTREXATE; CYTARABINE; **CAMPTOTHECIN**; CYCLOSPORINE A; SDZ PSC-833
IT Miscellaneous Descriptors
CAMPTOTHECIN; CYCLOSPORINE A; CYTARABINE; **GF 120918** ; HUMAN LYMPHOBLASTOID CELLS; METHOTREXATE; MULTIDRUG RESISTANCE; SDZ PSC-833
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hominidae
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 59-05-2 (METHOTREXATE)
147-94-4 (CYTARABINE)
7689-03-4 (CAMPTOTHECIN)
59865-13-3 (CYCLOSPORINE A)
121584-18-7 (SDZ PSC-833)

L154 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:161503 BIOSIS
DN PREV199598175803
TI DNA topoisomerases: Genome gate-keepers and their intruders, anticancer and antibacterial drugs.
AU Pommier, Yves
CS Lab. Mol. Pharmacol., Build. 37, Room 5C25, Natl. Cancer Inst., Natl. Inst. Health, Bethesda, MD 20892, USA
SO M-S (Medecine Sciences), (1994) Vol. 10, No. 10, pp. 953-955. ISSN: 0767-0974.
DT Article
Editorial
LA French
ED Entered STN: 11 Apr 1995
Last Updated on STN: 12 Apr 1995
CC Genetics - Plant 03504
Genetics - Animal 03506
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pharmacology - Drug metabolism and metabolic stimulators 22003
Neoplasms - Biochemistry 24006
Neoplasms - Therapeutic agents and therapy 24008
Genetics of bacteria and viruses 31500
Medical and clinical microbiology - Bacteriology 36002
Chemotherapy - Antibacterial agents 38504
Invertebrata: comparative, experimental morphology, physiology and pathology - Insecta: physiology 64076

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Pharmacology; Physiology; Tumor Biology
IT Chemicals & Biochemicals
DNA TOPOISOMERASES; VEPESID; DOXORUBICIN; MITOXANTRONE; **ACRIDINE**; ELLIPTICINE; **CAMPTOTHECIN**; TAXOL; TAXOTERE; CISPLATIN
IT Miscellaneous Descriptors
ACRIDINE; ANTINEOPLASTIC-DRUG; CAMPTOTHECIN; CISPLATIN; DNA RECOMBINATION; DOXORUBICIN; ELLIPTICINE; ENZYME INHIBITOR-DRUG; ENZYME MUTATION; EUKARYOTIC CELLS; MITOXANTRONE; QUINOLONES; TAXOL; TAXOTERE; VEPESID
ORGN Classifier
Diptera 75314
Super Taxa
Insecta; Arthropoda; Invertebrata; Animalia
Organism Name
Drosophila
Taxa Notes
Animals, Arthropods, Insects, Invertebrates
ORGN Classifier
Fungi 15000
Super Taxa
Plantae
Organism Name
fungi
yeast
Taxa Notes
Fungi, Microorganisms, Nonvascular Plants, Plants
ORGN Classifier
Mammalia 85700
Super Taxa
Vertebrata; Chordata; Animalia
Organism Name
mammals
Mammalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
ORGN Classifier
Poxviridae 03110
Super Taxa
dsDNA Viruses; Viruses; Microorganisms
Organism Name
vaccinia virus
Taxa Notes
Double-Stranded DNA Viruses, Microorganisms, Viruses
ORGN Classifier
Retroviridae 03305
Super Taxa
DNA and RNA Reverse Transcribing Viruses; Viruses; Microorganisms
Organism Name
human immunodeficiency virus
Taxa Notes
DNA and RNA Reverse Transcribing Viruses, Microorganisms, Viruses
RN 80449-01-0D (DNA TOPOISOMERASES)
33419-42-0 (VEPESID)
23214-92-8 (DOXORUBICIN)
65271-80-9 (MITOXANTRONE)

260-94-6 (ACRIDINE)
519-23-3 (ELLIPTICINE)
7689-03-4 (CAMPTOTHECIN)
33069-62-4 (TAXOL)
114977-28-5 (TAXOTERE)
15663-27-1 (CISPLATIN)

L154 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:19629 BIOSIS
DN PREV199598033929
TI DNA topoisomerases and topoisomerase inhibitors.
AU Giaccone, G.
CS Dep. Oncol., Free Univ. Hosp., De Boelelaan 1117, 1081 HV Amsterdam, Netherlands
SO Pathologie Biologie, (1994) Vol. 42, No. 4, pp. 346-352.
CODEN: PABIAQ. ISSN: 0369-8114.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 11 Jan 1995
Last Updated on STN: 23 Feb 1995
AB DNA topoisomerases are ubiquitous nuclear enzymes, essential for several steps of DNA metabolism. They have recently been shown to be specific targets of a number of anticancer agents. In this review are discussed the most recent discoveries in the physiology and the molecular biology of DNA topoisomerases, and the mechanism of interaction with drugs. In addition, alterations of DNA topoisomerases are also described, as potential responsible of drug resistance.
CC Cytology - Animal 02506
Cytology - Human 02508
Genetics - Animal 03506
Genetics - Human 03508
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808
Pathology - Necrosis 12510
Pathology - Therapy 12512
Metabolism - Nucleic acids, purines and pyrimidines 13014
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Metabolism; Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
DNA TOPOISOMERASES; TOPOISOMERASE; DOXORUBICIN; DAUNORUBICIN; IDARUBICIN; VP-16; VM-26; AMSACRINE; **ACRIDINE**; MITOXANTRONE; BISANTRENE; MERBARONE; SURAMIN; ACTINOMYCIN D; **TOPOTECAN**; 9-AMINO-CAMPTOTHECIN
IT Miscellaneous Descriptors
ACRIDINE CARBOXAMIDE; ACTINOMYCIN D; AMSACRINE; ANTHRAPYRAZOLE; ANTINEOPLASTIC-DRUG; ANTINEOPLASTIC-DRUG VM-26; BISANTRENE; CANCER; CELL DEATH; DAUNORUBICIN; DNA METABOLISM; DOXORUBICIN; IDARUBICIN; MERBARONE; MITOXANTRONE; SURAMIN; **TOPOTECAN**; VP-16; 2-METHYL-9-HYDROXYELLIPTICINE; 9-AMINO-CAMPTOTHECIN
ORGN Classifier
Hominidae 86215

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      Super Taxa
         Primates; Mammalia; Vertebrata; Chordata; Animalia
      Organism Name
         human
      Taxa Notes
         Animals, Chordates, Humans, Mammals, Primates, Vertebrates
ORGN Classifier
         Rodentia   86265
      Super Taxa
         Mammalia; Vertebrata; Chordata; Animalia
      Organism Name
         rodent
         Rodentia
      Taxa Notes
         Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
         Rodents, Vertebrates
RN    80449-01-0D (DNA TOPOISOMERASES)
      80449-01-0 (TOPOISOMERASE)
      23214-92-8 (DOXORUBICIN)
      20830-81-3 (DAUNORUBICIN)
      58957-92-9 (IDARUBICIN)
      33419-42-0 (VP-16)
      29767-20-2 (VM-26)
      51264-14-3 (AMSACRINE)
      260-94-6 (ACRIDINE)
      65271-80-9 (MITOXANTRONE)
      78186-34-2 (BISANTRENE)
      97534-21-9 (MERBARONE)
      145-63-1 (SURAMIN)
      50-76-0 (ACTINOMYCIN D)
      123948-87-8 (TOPOTECAN)
      91421-43-1 (9-AMINO-CAMPTOTHECIN)


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